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VACCINES AND THE AUTISM EPIDEMIC: REVIEWING THE FEDERAL GOVERNMENT'S TRACK RECORD AND CHARTING A COURSE FOR THE FUTURE

HEARING

BEFORE THE

COMMITTEE ON GOVERNMENT REFORM

HOUSE OF REPRESENTATIVES

ONE HUNDRED SEVENTH CONGRESS

SECOND SESSION

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CONTENTS

Page

Hearing held on December 10, 2002 1

Statement of:

- Baskin, David, M.D., professor of neurological surgery, Baylor College of Medicine, Houston, TX; Mark Geier, M.D., Ph.D., Genetic Consultants of Maryland, Bethesda, MD; and Walter Spitzer, M.D., M.P.H., F.R.C.P.C., emeritus professor of epidemiology, McGill University, Montreal, Canada 30
- Midthun, Karen, M.D., Director, Office of Vaccines Research and Review, Food and Drug Administration, Rockville, MD; Stephen Foote, Ph.D., Director, Division of Neuroscience and Basic Behavioral Science, National Institute of Mental Health, Bethesda, MD, accompanied by Christopher Portier, Ph.D., Director, Environmental Toxicology Program, National Institute of Environmental Health Sciences, Bethesda, MD 122

Letters, statements, etc., submitted for the record by:

- Baskin, David, M.D., professor of neurological surgery, Baylor College of Medicine, Houston, TX, Lancet article 34
- Burton, Hon. Dan, a Representative in Congress from the State of Indiana, exhibit 3 150
- Clay, Hon. Wm. Lacy, a Representative in Congress from the State of Missouri, prepared statement of 172
- Foote, Stephen, Ph.D., Director, Division of Neuroscience and Basic Behavioral Science, National Institute of Mental Health, Bethesda, MD, prepared statement of 143
- Geier, Mark, M.D., Ph.D., Genetic Consultants of Maryland, Bethesda, MD, prepared statement of 51
- Kucinich, Hon. Dennis J., a Representative in Congress from the State of Ohio, prepared statement of 10
- Maloney, Hon. Carolyn B., a Representative in Congress from the State of New York:
  - Washington Post article 16
  - Prepared statement of 20
  - New York Times editorial 14
- Midthun, Karen, M.D., Director, Office of Vaccines Research and Review, Food and Drug Administration, Rockville, MD, prepared statement of ... 125
- Spitzer, Walter, M.D., M.P.H., F.R.C.P.C., emeritus professor of epidemiology, McGill University, Montreal, Canada, prepared statement of 109

VACCINES AND THE AUTISM EPIDEMIC: REVIEWING THE FEDERAL GOVERNMENT'S TRACK RECORD AND CHARTING A COURSE FOR THE FUTURE

TUESDAY, DECEMBER 10, 2002

HOUSE OF REPRESENTATIVES,
COMMITTEE ON GOVERNMENT REFORM,
Washington, DC.

The committee met, pursuant to notice, at 1:30 p.m., in room 2154, Rayburn House Office Building, Hon. Dan Burton (chairman of the committee) presiding.

Present: Representatives Burton, Weldon, Waxman, Maloney, Kucinich, Tierney, and Green.

Staff present: Kevin Binger, staff director; Pablo Carrillo, counsel; S. Elizabeth Clay and John Rowe, professional staff members; Blain Rethmeier, communications director; Allyson Blandford, assistant to chief counsel; Robert A. Briggs, chief clerk; Robin Butler, officer manager; Joshua E. Gillespie, deputy chief clerk; Michael Layman, Susie Schulte, legislative assistants; Nicholis Mutton, deputy communications director; Leneal Scott, computer systems manager; Mindi Walker, staff assistant; Corinne Zaccagnini, systems administrator; T.J. Lightle, systems administrator assistant; Sarah Despres, minority counsel; Ellen Rayner, minority chief clerk; and Jean Gosa and Earley Green, minority assistant clerks.

Mr. BURTON. Good afternoon. A quorum being present, the Committee on Government Reform will come to order. I ask unanimous consent that all Members and witnesses' written and opening statements be included in the record. And without objection so ordered. I ask unanimous consent that all articles, exhibits and extraneous or tabular material referred to be included in the record. And without objection so ordered.

Because my good friend Mr. Waxman has to leave at 2 and because my opening statement is going to include a couple of clips on video, I've asked him if he'd like to go ahead and make his opening statement first, and he'd like to do that. So we'll let him start off and then I'll go into the details I want to go into in my opening statement.

Mr. Waxman.

Mr. WAXMAN. Thank you, Mr. Chairman, for the courtesy of allowing me to go first in the opening statements. There is a Democratic Caucus meeting at the same time as this committee hearing and it's unfortunate the scheduling conflict exists. So I wanted to make my opening statement. I unfortunately won't be able to be here for the testimony of many of the witnesses.

Mr. Chairman, in my lifetime polio has gone from every parents' fear to being a distant memory. Measles epidemics are few and far between. Congenital rubella, which can cause blindness, deafness, and autism, is increasingly rare. In just the last decade the most common causes of bacterial meningitis in young children have been controlled. We have vaccines to thank for these incredible accomplishments.

While millions of American children have been protected by immunization, no vaccine is 100 percent safe. The government must ensure that these vaccines are as safe as they can be, insist that vaccines are only administered when the benefit greatly outweighs the risk, and provide those who are injured with quick and fair compensation.

Today's hearing will focus on the allegation that routine childhood immunizations cause autism. Too often in this debate, though, solid public health information gets lost among sensational allegations or in recent days disgraceful political acts that are intended to protect special interests. This committee, unfortunately, has played a role in sowing confusion.

Mr. Chairman, I think you've been well intentioned in your efforts and genuine in your convictions, but often your theories have just been wrong. Two years ago, for instance, this committee publicized allegations that the measles-mumps-rubella, MMR, vaccine causes autism. This allegation frightened many parents. But the allegation has been disproven by scientific evidence. Studies in Europe and here in the United States by the Institute of Medicine have concluded that the MMR vaccine is not associated with autism and there should be no confusion about that.

Mr. Chairman, you've repeatedly, and rightly in my view, asked for more scientific studies so that we can know as much as possible about any adverse health consequences from vaccines. But it's important for our committee to pay attention to those studies once they are completed. In fact, it's important that parents know about two recently concluded peer-reviewed research reports. The first, which appeared in a recent issue of New England Journal of Medicine, examined the theory that the measles-mumps-rubella vaccine causes autism. Concerns about a potential link have terrified British parents and have resulted in measles outbreaks in the United Kingdom because of the children who are not getting vaccinated.

At previous committee hearings some Members and witnesses have called for a comparison between vaccinated and unvaccinated children in testing the safety of this vaccine. Well, this comparison is exactly what the New England Journal of Medicine study provides. It found no increase in autism among those children who were vaccinated compared to those who were not. The commentary that accompanied the study said that this study should put to rest parents' concerns over the safety of the MMR vaccine.

A second peer-reviewed research report was published in the Lancet 2 weeks ago. This study addressed the theory that thimerosal, a mercury based vaccine preservative, causes children to suffer neurological damage, including autism. In this study researchers measured the amount of mercury in the bloodstream of recently vaccinated infants. They found that this level does not exceed safe values in any child. The commentary that accompanied this study said it provided, “comforting reassurance.” It should be reassuring to parents that thimerosal has been removed from all routine vaccine immunizations except for the recently recommended flu vaccine and that additional studies on thimerosal are under way. These two research reports, with more research under way, are good news for public health. And I ask that these studies and the commentaries be included in the record.

Mr. Chairman, if I——

Mr. BURTON. Without objection.

Mr. WAXMAN. Thank you. The vaccines are an essential part of child health and parents should know that leading experts such as the CDC and the American Academy of Pediatrics continue to recommend that children receive all vaccines currently approved for routine use.

Now, I know that we have witnesses today who are going to include—the list of witnesses are going to include some scientists that dispute these findings. Now, that’s appropriate for them to dispute the findings. And in fact many of them dispute the findings at the peer-reviewed meetings that resulted in these two studies. If scientists have scientific arguments, they should take it up with their scientific peer members. That’s how scientific evaluation proceeds: Theories, evidence, contradictions, discussions, and then a consensus and then a challenge to that consensus. But this committee and politicians in the Congress are not the ones to make scientific decisions. And those who are in the minority and disagree with the scientific conclusions of their peers should challenge their peers by additional scientific arguments in evidence. I want to make that point very, very clearly, because what we have in this hearing is one of a series of hearings where we had a political argument that’s being made which seems to be refuted by the scientific evidence, and the answer to that is more political arguments and hearings, and I fear that these hearings only scare people without scientific arguments to back them up.

Now, the bad news for vaccine safety—the good news is these two studies reassure us about the vaccines, but the bad news for vaccine safety, however, has come on the political front. During the recent passage of the homeland security bill the Republican leadership snuck in two vaccine-related provisions that help industry and do nothing to help people who are injured by vaccines. The first of these provisions gave manufactures of the smallpox vaccine and hospitals that administer the vaccine virtually complete immunity from lawsuits but does nothing to compensate people who suffer vaccine-related injuries or death. The net result is that Republicans have managed to protect everyone but those who need the protection the most. Imagine an emergency room worker who is vaccinated against smallpox in order to protect the rest of us in case of a bioterrorist attack. If this hero or heroine on the front lines become incapacitated by the vaccine, he or she has no guarantee of compensation for his or her sacrifice. This is completely unacceptable.

Republicans also snuck in another vaccine-related provision into the homeland security bill that has no bearing on homeland security whatsoever. It provides liability protection for Eli Lilly, a manufacture and distributor of thimerosal. The provision was cherry picked from a list of recommendations made by an expert panel that overseas the Vaccine Injury Compensation Program. Not included in the homeland security bill were those recommendations made by this same expert panel that helped families and children, including increasing the death benefit, doubling the statute of limitations for the program, and allowing the program to pay for family counseling.

Here's a telling fact: The Republican leadership is so embarrassed by what they did that they won't even admit about what they've done. After the thimerosal provision was put in the bill, House Majority Leader Dick Armey said the provision was put in at the request of the White House. But when I wrote to the White House about this the White House claimed the idea originated in Congress. But to this day, not a single Member of the Republican leadership will admit responsibility for this provision.

I don't know what kind of values these actions represent, but they are not the values that I want to have any part of. They put the interests of powerful and wealthy special interest ahead of families with children suffering from debilitating illnesses. This is an embarrassment to the Congress and to our great country.

As we revisit these issues in the next Congress I hope that Republicans when considering changes to the Vaccine Injury Compensation Program do not forget that the purpose of the program is to help families not just to reduce the liability for industry; I also hope that the politics of vaccine safety reinforce rather than undermine the success of immunization. The lesson from the homeland security bill is not that people should fear that the smallpox vaccine is always dangerous or believe the allegations that thimerosal causes autism; the lesson is that protecting industry alone is unacceptable, both as public policy and principle.

I thank the witnesses that are going to be here today—I know this is a hearing where they've been asked to testify. I'm going to have a chance to review the record of the testimony. And I'll look forward to reviewing the record but I want to underscore again scientific issues should be decided by scientific principles and evidence, not by politics and not by presenting discredited minority views that have not yet been able to prevail in scientific evaluation as if they were fact and as a result scare a lot of people to do something that would be more harmful than helpful.

Thank you very much, Mr. Chairman, for your courtesy in allowing me to make this statement, and I'll look forward to reviewing the record.

Mr. BURTON. Let me just say before Mr. Waxman leaves he's been a big help in trying to change the vaccine injury compensation fund to be more responsive, and I do appreciate that. The one thing that I would like to say though is that Mr. Waxman does have a lot of other responsibilities and as such he has had to leave a number of times before we go into the details about scientific research that shows conflicting information. And I know that he reads these documents but I think sitting here and hearing the scientists from around the world that we've had come before us might give you a little different perspective, and I'm very sorry that you're not going to be able to be here today and have not been here for some of the witnesses that I think might have piqued your interest, maybe dissuaded you from some of the positions you've taken. Nevertheless, you're my buddy. I'm glad you work with me.

Mr. WAXMAN. Will you yield to me? Thank you very much for your comments. I have had a chance to review the testimony of witnesses. I've had my staff very much involved in this issue. I've been involved in vaccine issues for at least 20 years in the Congress of the United States. And if you come in with a preconceived idea and hear witnesses say what you believe to be the case, I'm sure it reaffirms your views. But I think still these issues of science ought to be decided by the scientific method. That's the thing that's going to protect us.

I thank you for letting me make the statement.

Mr. BURTON. I will send to your office, it will only take you about 20 minutes, I have a couple of tapes I would like for you to take a look at.

I will let Mr. Weldon go next and I'll let my colleagues speak as well because I am going to take a little bit of time about my opening statement. I don't want to be discourteous to them. So Dr. Weldon.

Mr. WELDON. Thank you, Mr. Chairman. And I want to commend you for calling this hearing and I specifically want to commend you for your willingness to explore this issue. If scientists behaved purely like scientists and did purely objective research all the time, then the comments made by Mr. Waxman would be valid. The reality is scientists and medical researchers operate with a system of biases that frankly can be very, very politicized. And the claims that were made by the ranking member that these issues essentially have been put to rest I don't believe are valid. Specifically when you look at the issue of the MMR, the Danish study, the data from the Danish study which he was referring to, which I'm sure we're going to hear more about today from our witnesses, was valuable but it didn't really get at answering the question of really looking at kids with regressive autism. I don't think the opinion of this committee has ever been that mercury per se or the MMR per se causes autism, and I think the general consensus of scientific opinion is that this is probably a multifactorial disease. And while the Danish study provided some valuable information, really it didn't answer the question, I think, of regressive autism.

And the other thing that was very disturbing about the Danish study is they documented a tenfold increase in the incidence of autism in Denmark. There's absolutely no comment in the New England Journal about that issue.

And let me just say I share Mr. Waxman's sentiments on vaccines. Vaccinations and septic systems have probably done more to save hundreds of millions of lives in the civilized world than anything else, and we all need to be very, very grateful to these tremendous breakthroughs in vaccinations. But there's, I think, some very, very troubling issues that have not been resolved. The thing that I continue to find extremely disturbing is the fact that the CDC still does not allow researchers access to the vaccine safety data. If everything was so objective and any scientist at all can look at this stuff, it would be one thing, but they continue to deny people access to this information. And until we get a free and open dialog within the scientific community, I don't think, for one, I will ever be satisfied that there isn't some data suggesting that some children may have serious side effects from some of these vaccines that is really going undetected, unnoticed and they may actually cause autism.

Let me just conclude by saying that the issue with the MMR that got all this started was a clinical study, and the Danish study is again another epidemiologic study. And a clinical study is very, very cheap and easy to do but nobody seems to want to do it. We had somebody at one of our previous hearings, a Dr. Kriegsman from New York, who had replicated some of Wakefield's work showing that these kids are developing inflammatory bowel disease, and then he wanted to do the next step, he wanted to actually do the pathologic analysis on these biopsy specimens, and the institution that he worked at said, no, they don't want to get into it, this is too controversial.

So if everything was so objective and scientific like Mr. Waxman is saying, why do you have a major institution in New York City saying, no, we don't want to get into that?

You know, to a certain extent the problem is we're trying to investigate a sacred cow. For a lot of people in the medical community, there's this tremendous fear. If you say anything negative about vaccines, then parents will stop vaccinating their kids and then you'll have all these outbreaks of these diseases. I don't think parents are that stupid. I think parents will continue to vaccinate their kids. We have a responsibility to them to really find out if there's truth in all this. I don't think the answers are in, and I don't think this mercury study really helps us that much either. It provides—let my just say it's a great study and we're going to hear more about the mercury study because it gives us data in an arena where we had no data, so I'm thankful for that, but basically studies 40 kids. We don't know if the kids that get autism in response to mercury are kids who don't handle the mercury properly. And I don't think the ranking member was accurate at all to say that this puts this issue to rest. Frankly, I've been very, very surprised at his attitude in all this because before I got here I had an image of him as being somebody who would really go after all these toxin issues and all these pollution issues, and ethyl mercury, which is what thimerosal disassociates into, is chemically very, very similar to methyl mercury in its structure. It's very, very bothersome when you follow the vaccine—well, it's not in the vaccines anymore, but a few years ago when you followed the vaccine schedule you were giving kids doses 10, 20, 30 times the toxic dosage for these kids. And the recent—I guess it was in the Lancet study that looked at these kids and looked at excretions, I think it was a very valuable study but it doesn't answer the question that the kids that become autistic may be the kids that don't process the thimerosal properly, and that study only had 40 kids in it.

So I say to you, Mr. Chairman, keep it up. I would like to see you get a subcommittee chairmanship in the next Congress and I'd like you to continue pushing this vaccine safety issue until we get answers to some these questions, until the CDC starts opening up that VSD data to independent researchers. You know, in Florida we have this thing called a sunshine law. What everybody says is sunshine is the best antiseptic. The best way to get answers on the vaccine safety data is to open it up and let objective scientists come in and look at it. If these vaccines aren't that safe then that will be validated.

I think I've gone more than 5 minutes, Mr. Chairman. I want to thank you. I yield back.

Mr. BURTON. Just to followup on what you said, the Justice Department filed a motion asking the Special Master to keep all information secret, and that follows along with what you're talking about. That's very disconcerting to me.

Mr. WELDON. Mr. Chairman, if I could just interject one other point. I objected to the language that was put in the Homeland Security Act on protecting the vaccine producers. And you know, Mr. Waxman just said that these studies show that it's safe and then he criticized us for protecting, he criticized Republican leadership for protecting the manufacturers. If what he said is true, that they're safe, then why should he be critical of us protecting the manufacturers? The truth is that language shouldn't have been in there. I objected to it and I think you objected to it as well, and it was a Member of the Senate who put that language in there. And I'm ready to work with Mr. Waxman and all the other Members on the minority side when we try to move that vaccine safety bill in the next Congress. I know Senator Snowe is very, very interested in doing something about this, and I think we can fix this issue.

And the one thing that Mr. Waxman said which is correct is that we need to make sure the kids are protected. But I might say that if mercury isn't a problem and if MMR isn't a problem, then, you know, why should he be concerned that language was in there? I think the language should be changed. I'm ready to work with you, Mr. Chairman and Mr. Waxman, to try to fix it.

Mr. BURTON. Very good. Mr. Kucinich.

Mr. KUCINICH. As I listen to the debate and have listened to it over this past year between two individuals who I respect most highly in this Congress, Chairman Burton and Mr. Waxman, it causes me to reflect on how is it possible that you can get two people who care so much about this country and whose dedication to the people is unquestioned and revered, how Mr. Waxman, for example, who's been the champion in Congress in challenging the tobacco companies, long before anyone thought about it, understood the health questions that were involved, and built a national reputation around that. And on the other hand you have Chairman Burton, who I happen to believe has been far ahead of the rest of the country in raising issues about the safety of vaccines, and rightly so, how is it you can get this kind of conflict.

Here's how I think it happens: There are really profoundly different philosophical views on how knowledge is organized and I think it is reflected here, and I think it's worth thinking about when we think about the debate that goes on here. One approach deals in allopathic medicine, another one respected holistic medicine. One approach is linear, the other one is nonlinear in its thinking. One is rational, the other one is intuitive. The one approach is deductive, the other one is inductive. Neither is wrong. They're just simply different ways of looking at the world. They often can lead to the discovery of matters that are urgent to the public interest, which is why I'm here to state my support for the efforts of Chairman Burton. He's been courageous and he has gone forward with dedication and persistence, and his commitment to the search for a cause for autism has provided leadership toward a goal that will eventually help not only his own family but also thousands of individuals with autism throughout the world.

I want to thank the witnesses who have researched studies and experienced firsthand the effects of autism. As you know, autism spectrum disorders present a significant problem to our youth. The Centers for Disease Control estimates almost 400,000 children are affected by autism. Equally disturbing are estimates by the International Child Development Resource Center that autism-related costs will exceed 1 trillion in the next 50 years. $1 trillion. As the rates of autism appear to be increasing in many States, autism presents a problem of profound significance to all of us. It is essential that we continue to address this issue.

The NIH has taken significant steps to find answers with an international effort that brought together researchers from Canada, Britain, France and Germany to study causes and mechanisms of autism. From this research theories about the connection between autism and vaccines are being developed, providing possible clues that bring us closer to the answers we seek. The NIH should be applauded for these efforts. At the same time we must recognize the research is ongoing. It is by no means complete.

The Institute of Medicine reports that the report that was published last year concluded, "the evidence is inadequate to accept or reject a causal relationship between exposure to thimerosal from vaccines and neurological development, disorders of autism, ADHD, speech and language delays." It also called for more research. From this report and other recent research it could be possible that thimerosal is a contributing factor in autism. And unless we have forums like this, there is no way to move that discussion and that effort forward.

With these conclusions in mind, it's unjust that an exemption has been provided to vaccine manufacturers in the homeland security bill in sections 1714 to 1717. This exemption will effectively shield vaccine manufacturers from lawsuits from claimants that allege injury from thimerosal containing vaccines. Even those claimants involved in pending litigation will be forced to drop their lawsuits and begin a new process through the Vaccine Injury Compensation Program. While I believe that the Vaccine Injury Compensation Program is largely a good program, it is in need of reform and I support the chairman's legislation to make needed reform, H.R. 3741.

The exemption that slipped into the homeland security bill will deny many thimerosal injury claimants redress because the current law governing the Vaccine Injury Compensation Program imposes a 3-year statute of limitations. This will restrict the number of claimants that can seek redress for their injuries. The overall effect of the sections 1714 to 1717 will be that many claimants will be prevented from seeking recourse through the judicial system and some claimants are prevented from any sort of redress. Meanwhile, manufacturers that are ultimately responsible will be shielded from that responsibility. Both the substance of these provisions and the process in which they were added were wrong.

I know, Mr. Chairman, you share my concerns. You addressed these passionately on the floor of the House and addressed to the House on the day that the House passed the homeland security legislation and emphasized over and over these same points. This committee has investigated this issue in depth over the past 3 years. Should this committee have introduced legislation to repeal sections 1714 to 1717? And I hope the committee takes the lead on this issue.

Well, sections 1714 to 1717 may be just one issue of the many that this committee has investigated relating to autism. I look forward to reading the testimony of the witnesses as it relates to several vaccines and the work of a number of government agencies.

I thank the witnesses for their work, hope to continue to improve the way our government addresses autism and want to say that I am proud to be on a committee that is chaired by Dan Burton and I'm proud to be brought to this committee by my dear friend Henry Waxman. Thank you very much.

[The prepared statement of Hon. Dennis J. Kucinich follows:]

not included in [illegible]

(Prepared)

Opening Statement
Rep. Dennis Kucinich
December 10, 2002

"Vaccines and the Autism Epidemic: Reviewing the Federal Government's Track Record and Charting a Course for Action in the Future"

I would like to begin by thanking Chairman Burton for his dedication and persistence on the issue of autism. His commitment to the search for a cause for autism has provided leadership toward a goal that will eventually help not only his own family, but also thousands of individuals with autism throughout the world. My thanks also to the witnesses, who have researched, studied, and experienced firsthand the effects of autism.

As you all know, autism spectrum disorders present a significant problem to our youth. The Center for Disease Control estimates that almost 400,000 children are affected by autism; equally disturbing are estimates by the International Child Development Resource Center that autism-related costs will exceed $1 trillion in the next fifty years. As the rates of autism appear to be increasing in many states, autism presents a problem of profound significance to all of us. It is essential that we continue to address this issue.

The National Institutes of Health has taken significant steps to find answers with an international effort that has brought together researchers from Canada, Britain, France, and Germany to study causes and mechanisms of autism. From this research, theories about the connection between autism and vaccines are being developed, providing possible clues that bring us closer to the answers we seek. The NIH should be applauded for these efforts.

At the same time, we must recognize that this research is ongoing. It is by no means complete. The Institute of Medicine report that was published last year concluded: "the evidence is inadequate to accept or reject a causal relationship between exposure to thimerosal from vaccines and neurological development disorders of autism, ADHD, and speech and language delays." It also called for more research. From this report, and other recent research, it could be possible that thimerosal is a contributing factor in autism.

With these conclusions in mind, it is unjust that an exemption has been provided to vaccine manufacturers in the Homeland Security bill in sections 1714-1717. This exemption will effectively shield vaccine manufacturers from lawsuits from claimants that allege injury from thimerosal-containing vaccines. Even those claimants that are involved in pending litigation will be forced to drop their lawsuits and begin a new process through the Vaccine Injury Compensation Program. While I believe that the Vaccine Injury Compensation Program, VICP, is largely a good program, (it is in need of reform, and I support the Chairman's legislation to make needed improvements, HR 3741.) The exemption slipped into the Homeland Security bill will deny many thimerosal injury claimants redress because the current law governing the VICP imposes a 3-year statute of limitations. This will restrict the number of claimants that can seek redress for their injuries.

The overall effect of sections 1714-1717 will be that many claimants will be prevented from seeking recourse through the judicial system, and some claimants are prevented from any sort of redress. Meanwhile, manufacturers that are ultimately responsible will be shielded from that responsibility. Both the substance of these provisions and the process in which they were added are wrong.

I know, Mr. Chairman, that you share my concerns, addressed to the House on the day that the House passed the Homeland Security legislation, and emphasized these same points. This committee has investigated this issue in depth over the past 3 years. Shouldn't this committee introduce legislation to repeal sections 1714-1717? Shouldn't it be this committee that takes the lead on this issue?

While sections 1714-1717 may be just one issue of the many that this committee has investigated relating to autism, I look forward to the testimony of the witnesses as it relates to several vaccines and the work of a number of government agencies. I thank the witnesses for their work and hope to continue to improve the way our government addresses autism.

Mr. BURTON. Thank you very much. Mrs. Maloney.

Mrs. MALONEY. Thank you, Mr. Chairman. I'd like to thank you and Ranking Member Waxman for focusing on this important issue. I would especially like to thank you, Chairman Burton, for your determination, courage and long time commitment to investigating an issue that I know is very personal to him, autism. May I also say that I have often been on the other side of issues with Chairman Burton. We don't always agree, but I have seen his dogged determination firsthand and if anyone can get to the truth on this issue, he can, and I applaud your effort, Chairman Burton.

I have understood from the Republican staff that in his opening statement the chairman will detail a chronology of events surrounding autism research and the role of the Federal Government. But I do not believe that his presentation will include what I think was an outrageous abuse of legislative power, the Majority Leader Dick Armey's gift to Eli Lilly that added last minute provisions in the Department of Homeland Security bill. These provisions that were added in the dark of night deny families of autistic children the right to file suits seeking compensation from manufacturers of thimerosal.

Let me be very clear the new law blocks pending litigation against the manufacturers of this mercury based preservative, thimerosal, being brought by the families of autistic children. The new law forces families to seek relief from the Vaccine Injury Compensation Program. The New York times called the leadership's late addition, "an abuse of congressional process." And I believe this is an understatement and I request unanimous permission to place in the record the editorial from the Times.

Mr. BURTON. Without objection, we'll do that.

[The information referred to follows:]

14

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The New York Times

December 5, 2002, Thursday, Late Edition - Final

SECTION: Section A; Page 42; Column 1; **Editorial** Desk

LENGTH: 401 words

HEADLINE: Fanning **Vaccine** Fears

BODY:
The recent backroom political maneuver that gave Eli Lilly protection against lawsuits for damage allegedly caused by a mercury-containing preservative in **vaccines** was not only an abuse of Congressional process. Its more pernicious effect was to fan fears about the safety of **vaccines** and the ingredients used to protect them from dangerous contamination.

The preservative in question, known as thimerosal, was used in many **vaccines** to prevent microbial contamination until concerns were raised in 1999 that cumulative doses of mercury might cause subtle harm to the developing brain. Since then, thimerosal has been dropped from the **vaccines** routinely administered to infants in America, but the issue remains important because thousands of parents whose children had previously received mercury-containing **vaccines** have filed damage claims or lawsuits alleging harm. Although mercury is known to be toxic at high doses, there is very little data on whether very low doses of ethyl mercury, the form found in thimerosal, can be harmful. Last year the Institute of Medicine, an arm of the National Academy of Sciences, concluded that the scientific evidence neither proved nor disproved a link between thimerosal and neurodevelopmental disorders in children. But this year the World Health Organization endorsed the preservative for global use, concluding that there is no evidence of toxicity in infants, children or adults exposed to thimerosal in **vaccines.** That judgment was buttressed by an encouraging study published last Saturday in The Lancet, a British medical journal. It found that **vaccines** containing thimerosal did not raise the amount of mercury in infants above federal safety limits and that the mercury was excreted quickly, suggesting that it would not accumulate with repeated **vaccine** injections and cause damage.

Whatever risks might be posed by thimerosal are remote compared with the risk from not getting vaccinated. That is why the American Academy of Pediatrics recommended this week that infants as young as six months be given influenza **vaccine**, which still contains small amounts of thimerosal. The academy said healthy infants were at relatively high risk of hospitalization for the flu; thus the benefits of vaccination "outweigh the theoretical risk of adverse effects, if any, from the small volume of thimerosal" in the **vaccine.** http://www.nytimes.com

LOAD-DATE: December 5, 2002

Mrs. MALONEY. Another quote was included in yesterday's Washington Post. Donna Brinker, the mother of an autistic son named Thomas, said, "I believe in protecting our homeland but it petrifies me to think that our nation would protect any industry at the expense of our children." And, Mr. Chairman, I would like to add yesterday's Post story likewise to the record.

[The information referred to follows:]

Washington Post, 12/9/02

washingtonpost.com

New Vaccine Clause Angers Parents of Autistic

Amendment Buried in Homeland Security Law Restricts Right to Sue Makers of Drug Preservative

By Susan Warner
Special to the Washington Post
Monday, December 9, 2002; Page A03

Thomas Brinker loves to sing and play with string. He watches ABC News anchor Peter Jennings on television every night and shouts: "Tickle Peter Jennings." He's 8 now, but his attention span is short and his temper flares easily.

Thomas has autism, a condition his parents believe was caused by a simple childhood immunization. "We're waiting for his first normal moment," said his mother, Donna Brinker of Glen Mills, Pa.

It was Donna Brinker's temper that flared when she learned that Congress had quietly restricted her right to sue Eli Lilly and Co. and other manufacturers of Thimerosal, the mercury-based vaccine preservative she believes caused her son's condition. The change came in two paragraphs tacked onto the massive Homeland Security Act just days before Congress approved the legislation in November.

The Brinkers are among 800 families in more than a dozen states that have filed similar cases seeking compensation for the costs of their children's autism. Under the new law, signed by President Bush Nov. 25, the parents are required to file claims with a special administrative court under the National Vaccine Injury Compensation Program before they can take their cases to civil court.

The changes could sharply reduce parents' chances of prevailing in civil courts, where damage awards normally could be much higher than those in the "vaccine court." The federal program covers claims for medical and education expenses, but damages for pain, suffering and death are limited to $250,000. Lawyers for the plaintiffs say their awards would likely be higher if they could first take their cases to state courts, where civil juries are known to award millions of dollars in medical injury cases.

Meanwhile, the Department of Justice has filed a request to restrict the use of information gathered in vaccine court proceedings in subsequent civil court cases, another potential obstacle for the plaintiffs.

"I felt betrayed," Brinker said of the new legislation. "I believe in protecting our homeland, but it petrifies me to think that our nation would protect any industry at the expense of our children."

Penny Starr-Ashton, of Drexel Hill, Pa., whose autistic 6-year-old daughter, Maddie, is another plaintiff in a class-action lawsuit filed in Pennsylvania in July, said it is particularly painful to have the provision wrapped in the flag.

"Who doesn't want a safer country?" she asked. "But who's going to protect me? Who's going to protect my child?"

The National Institute of Child Health and Human Development estimates that between 1 in 500 and 1 in 1,000 children is diagnosed with autism in the United States each year. Initial studies in the 1960s found four to five cases of autism in every 10,000 people, although the institute cautions that some of the increase could be due to changes in reporting and diagnosing the disease.

A study by the University of California at Davis found that a third of California parents of autistic children diagnosed in the mid-1990s blame vaccines for their children's illnesses.

Congress created the National Vaccine Injury Compensation Program in 1986 to address growing concerns about vaccine safety. Claims are filed with the Department of Health and Human Services through the U.S. Court of Federal Claims. The program has paid out 1,775 claims totaling $1.4 billion and is funded by a 75-cent surcharge on every child vaccination.

Brinker said parents of children with signs of mercury poisoning can spend up to $20,000 a year out of pocket. Thomas is undergoing chelation therapy to draw metals out of his body and is on a strict diet. His parents take him to a specialist in Louisiana for treatment, and his mother travels to Mexico to get drugs that are not approved in the United States.

Beyond today's expenses, Brinker worries about supporting Thomas in the long term. "The mercury preservative has deprived Thomas of having a normal life," she said. "That our nation would protect such a killer is beyond comprehension."

Aside from potentially lower awards, Thomas Brinker and Maddie Ashton will have another problem in vaccine court, said their lawyer, Tobi Millrood. Like many children, they were diagnosed with autism more than three years after their vaccinations, beyond the time permitted to file under the program's rules.

Some states, including Oregon, Florida, Louisiana, Illinois and California, had ruled that they had jurisdiction over Thimerosal cases, said John Kim, a Houston lawyer who argued against the government's request to close vaccine court records. "Now I guess this new provision in the Homeland Security Act trumps that," Kim said.

Meanwhile, all Thimerosal cases have been put on hold at vaccine court while the court grapples with the scientific debate over the possible causes of autism. The Office of the Special Master, which oversees procedural issues at vaccine court, expects 3,000 to 5,000 filings.

Parents outraged about the last-minute change point to Eli Lilly, the Indianapolis drug maker, as its biggest beneficiary. Lilly invented Thimerosal and manufactured it until the 1980s. The preservative is 50 percent mercury by weight, and had been used in vaccines since the 1930s. Lilly is a defendant in 200 Thimerosal-related lawsuits.

"It's turned into being about money," Brinker said. "Parents with kids with autism don't have the money to give to congressmen. It turns out whoever has the most money wins."

The provision in the Homeland Security bill was originally written by Sen. Bill Frist (R-Tenn.), a physician, as part of broader legislation aimed at helping drug companies produce vaccines after post-Sept. 11, 2001, concerns about smallpox and anthrax. The number of U.S. vaccine manufacturers has dropped to four, with companies complaining of low profit margins, manufacturing problems and fear of liability for injury.

Edward G. Sagebiel, a spokesman for Lilly, said his company had no role in pushing the last-minute legislative changes. "We express sympathy for the parents and the children who have suffered adverse reactions," he said. "However, the lawsuits that have been filed against Lilly and other manufacturers are not supported by science."

The House Government Reform Committee has scheduled a hearing on vaccine safety for Tuesday.

In 1999, the Food and Drug Administration conducted a review of Thimerosal and found no evidence of harm beyond limited cases of hypersensitivity to the vaccine. But the same year, the Academy of Pediatrics and the U.S. Public Health Service recommended that Thimerosal be removed from vaccines, partly out of

18

fear that parents would stop immunizing their children and create a bigger public health problem.

In October 2001, the Institute of Medicine, a branch of the National Academy of Sciences, said there was no evidence that Thimerosal caused autism, but it did say the theory was "biologically plausible."

Most recently, on Nov. 30, the British medical journal the Lancet published a study showing that infants who received vaccines containing Thimerosal had levels of mercury in their blood that are within federal limits.

Starr-Ashton remains unconvinced. "I don't believe anything that is 50 percent mercury by weight is safe," she said. She noted reports of health damage caused by mercury in fish, thermometers and dental fillings. "I'm not that dumb."

The debate over science has become a furor over the democratic process in the tight-knit community of parents of children with autism that is linked by the Internet and community support groups.

"Nobody is owning up to it," Brinker said. "It is so underhanded. I just can't believe our government would do this. We're not going to back down on this issue. We will not be silent."

Starr-Ashton said she is not against vaccines, especially because she taught in a school for the deaf for many years: "I saw first-hand the damage done by rubella."

But now she does not know who to trust. "Here I was, a dutiful parent taking my child to do what the government and the Academy of Pediatrics said I should do to protect my child against disease," Starr-Ashton said. "Something went terribly wrong. I need answers."

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Mrs. MALONEY. The Homeland Security bill was not the right place to change existing law governing vaccines and certainly not vaccines that have absolutely nothing, absolutely nothing to do with homeland security, and it certainly isn't the way to change existing law. Rewriting public policy in the middle of the night without proper notice, without regular order, without hearings, real legislative policy should not be made this way. It is inexcusable and flies in the face of the principles of open and just government.

Another part of the scandal, and I considered it a scandal, is for days we couldn't find out how this happened. At least and finally Mr. Armey finally came forward days later and claimed credit for the inclusion of the language at the request of the White House. I would not want to claim credit for what one editorial called, "sneaky, backhanded and anonymous." But what I would really like to know and to learn from these hearings is what is Eli Lilly, this pharmaceutical company, so worried about? Why do they need this new protection? Hopefully we will learn some of what they are worried about today from our distinguished panelists and scientists.

Autism and the growing rates of autism among our children is a serious issue that deserves sincere deliberation and attention from this Congress. I am proud to have been part of a bipartisan commitment and coalition that has worked for the past 5 years to double the funding for the National Institutes of Health, the research arm for health. We worked to double it from $13.6 billion in fiscal year 1998 and when we finally get a budget in 2003, if it goes forward as planned, it will have climbed to $27.3. The hope is that these strong investments in biomedical research will spur scientific advances that will ultimately translate into better health care for the American people, including a better understanding of autism and vaccine safety. We do not have a consensus in the scientific community as to the cause of autism. More research and funding is needed to investigate this troubling health issue.

I wholeheartedly support Chairman Burton's quality call for a White House conference on autism. We need continued robust research for the sake of our children. We need to know more. And I congratulate your efforts on focusing on this important health issue. Thank you, Mr. Chairman. I yield back the balance of my time.

[The prepared statement of Hon. Carolyn B. Maloney follows:]

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STATEMENT OF CONGRESSWOMAN CAROLYN B. MALONEY

Committee on Government Reform
Full Committee Hearing

"Vaccines and the Autism Epidemic:
Reviewing the Federal Government's Track Record and Charting a Course for the Future."

December 10, 2002

Thank you Mr. Chairman and Ranking Member Waxman.

I especially would like to thank Chairman Burton for his determination, courage and longtime commitment to investigating an issue that I know is very personal to him, autism.

May I also say that I have often been on the other side of issues from the Chairman. I have seen his dogged determination first hand and if any one can get to the truth on this issue, he can. I applaud your effort, Chairman Burton!

The Chairman in his opening statement detailed the chronology of events surrounding autism research and the role of the Federal government.

He alluded to the eleventh hour action by this Congress, and I guess more specifically Majority Leader Dick Armey's gift to Eli Lilly, that added last-minute provisions to the Department of Homeland Security bill. These provisions deny families of autistic children the right to file suits seeking compensation from manufacturers of Thimerosol.

Let me be plain, the new law blocks pending litigation against the manufacturers of this mercury-based preservative, Thimerosol, being brought by families of autistic children. The new law forces families to seek relief from the Vaccine Injury Compensation Program.

The New York Times called the Leadership's late addition, "an abuse of Congressional process." That is an understatement.

PRINTED ON RECYCLED PAPER

The better quote was included in yesterday's Washington Post. Donna Brinker, the mother of an autistic son named Thomas, said, (quote) "I believe in protecting our homeland, but it petrifies me to think that our nation would protect any industry at the expense of our children." (end quote) Mr. Chairman, I would like to add yesterday's Post story to the record.

The homeland security bill was not the right place to change existing law governing vaccines and certainly not vaccines that have absolutely nothing to do with national security.

And it certainly isn't the way to change existing law -- rewriting public policy in the middle of the night without proper notice, without regular order, without hearings. Real legislative policy should not be made this way, it is inexcusable and flies in the face of the principles of open government.

But the real scandal is that for days, we couldn't find out who did it!

I thought we might have to call on Sherlock Holmes to solve the mystery.

I'm waiting for the movie!

At least Mr. Armey finally came forward days later and claimed credit for the inclusion of the language at the request of the White House. I would not want to claim credit for what one editorial called "sneaky, back-handed and anonymous..." Hear. Hear.

What I would like to know is: What is Eli Lilly, this pharmaceutical company, worried about? Why do they need this new protection?

Hopefully we will learn some of what they are worried about today from our distinguished panelists.

Autism and the growing rates of autism among our children is a serious issue that deserves sincere, deliberate attention from this Congress.

I am proud to have been a part of the bipartisan commitment to doubling the National Institutes of Health (NIH) budget – from $13.6 billion in FY98 to $27.3 billion in FY03 (if we pass the appropriations bill). The hope is that these strong investments in biomedical research will spur scientific advances that will ultimately translate into better health care for the American people, including a better understanding of autism.

We do not have consensus in the scientific community as to the cause of autism. More research and funding is needed to investigate this troubling health issue. I wholeheartedly support Chairman Burton's call for a White House Conference on Autism.

But a sneaky midnight attack on seeking the truth and looking for causes will not work.

We need continued, robust research. For the sake of the children, we need to know more.

14th District • New York

Congresswoman

***Carolyn* Maloney**

Reports

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December 10, 2002
FOR IMMEDIATE RELEASE

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REP. MALONEY DENOUNCES "MIDNIGHT DEAL"

JOINS LAWMAKERS IN CALLING ON PRESIDENT TO HOST CONFERENCE ON AUTISM

Washington, DC – Today, Congresswoman Carolyn B. Maloney (D-NY) joined fellow lawmakers on the House Committee on Government Reform in condemning the House Leadership for adding last-minute provisions to the Homeland Security Bill designed to protect Eli Lilly from families with autistic children seeking compensation. In addition, she joined Chairman Dan Burton (R-IN) in urging the President to hold a White House Conference on autism.

"News reports called the Leadership's actions 'an abuse of Congressional process.' That is the understatement of the year. Real legislative policy is not made in the dead of night, nor should it be made at the expense of our children," said Congresswoman Maloney in a statement today.

In recent years the number of American children suffering from autism has risen significantly. A recent study funded by the State of California determined the number of autism cases in the state has tripled in the last 10 years. Based on statistics from the U.S. Department of Education and other governmental agencies, autism is growing at a rate of 10-17 percent per year.

For the full text of Congresswoman Maloney's statement, please go to: www.house.gov/maloney

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December 5, 2002 Thursday

SECTION: METRO - EDITORIAL; Pg. 6

LENGTH: 514 words

HEADLINE: Drug company security

BODY:

A massive homeland security bill that was adopted by Congress last month is supposed to protect the United States from terrorism, but it also protects large drug companies from a very different enemy: parents of children with autism.

A provision attached to the bill in the House at the last minute shields companies from lawsuits by parents who say a preservative in infant vaccines caused their children's developmental disorder.

Thimerosal, which contains mercury, was developed by Eli Lilly & Co. in the 1920s and was widely used in infant vaccines. The preservative enabled doctors to use the same vial of vaccine to inoculate many different children without risk of contaminating it. But some parents believe that mercury's presence in vaccines exposed their babies to damaging levels of what is, after all, a neurotoxin.

Studies thus far have not proved a link between thimerosal and autism. But such concerns were reinforced in 2000 when the Food and Drug Administration asked drug companies to stop using mercury-based preservatives in infant vaccines.

Now, though, legal options for families who believe that their children were harmed have been significantly curtailed. This amendment affords thimerosal the same liability protection enjoyed by vaccines.

Instead of being able to file suit in state court, parents will have to first go through the federal Vaccine Injury Compensation Program, a 14-year-old, no-fault system that provides limited compensation: medical costs and up to $ 250,000 for pain and suffering. If they are dissatisfied with the outcome, they can then file suit.

For some families, this is more than just another hoop to jump through. The federal program has a three-year statute of limitations. Many parents of autistic children did not suspect thimerosal until after that deadline passed. They are left without any recourse.

A case can be made for treating thimerosal as an intrinsic part of a vaccine, something that should properly be handled by the federal program. But it shouldn't have been done in this sneaky, back-handed and anonymous way. No one has admitted to attaching the rider. *

The matter should have been debated on its own merits, not buried in a nearly 500-page bill that the Senate was under enormous pressure to adopt before the end of the year.

Some of the amendment's defenders argue that the thimerosal question does have a bearing on homeland security since vaccines are needed to protect the nation from bioterrorism. But thimerosal isn't used in vaccines for anthrax or smallpox or other potential bioterrorist agents. And while a successful lawsuit could hurt a pharmaceutical company that manufactures needed vaccines, that's a pretty tenuous connection to homeland security.

The beneficiaries are big drug companies such as Eli Lilly, and it's a shame that efforts to strip it from the bill failed. Now, autistic children and their families will have to hope for fairer treatment next year, when Senate Majority Leader Trent Lott says that special interest provisions in the bill will be reworked.

LOAD-DATE: December 5, 2002

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The New York Times

December 5, 2002, Thursday, Late Edition - Final

SECTION: Section A; Page 42; Column 1; **Editorial** Desk

LENGTH: 401 words

HEADLINE: Fanning **Vaccine** Fears

BODY:

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The preservative in question, known as thimerosal, was used in many **vaccines** to prevent microbial contamination until concerns were raised in 1999 that cumulative doses of mercury might cause subtle harm to the developing brain. Since then, thimerosal has been dropped from the **vaccines** routinely administered to infants in America, but the issue remains important because thousands of parents whose children had previously received mercury-containing **vaccines** have filed damage claims or lawsuits alleging harm. Although mercury is known to be toxic at high doses, there is very little data on whether very low doses of ethyl mercury, the form found in thimerosal, can be harmful. Last year the Institute of Medicine, an arm of the National Academy of Sciences, concluded that the scientific evidence neither proved nor disproved a link between thimerosal and neurodevelopmental disorders in children. But this year the World Health Organization endorsed the preservative for global use, concluding that there is no evidence of toxicity in infants, children or adults exposed to thimerosal in **vaccines.** That judgment was buttressed by an encouraging study published last Saturday in The Lancet, a British medical journal. It found that **vaccines** containing thimerosal did not raise the amount of mercury in infants above federal safety limits and that the mercury was excreted quickly, suggesting that it would not accumulate with repeated **vaccine** injections and cause damage.

Whatever risks might be posed by thimerosal are remote compared with the risk from not getting vaccinated. That is why the American Academy of Pediatrics recommended this week that infants as young as six months be given influenza **vaccine,** which still contains small amounts of thimerosal. The academy said healthy infants were at relatively high risk of hospitalization for the flu; thus the benefits of vaccination "outweigh the theoretical risk of adverse effects, if any, from the small volume of thimerosal" in the **vaccine.** http://www.nytimes.com

LOAD-DATE: December 5, 2002

Mr. BURTON. Thank you, Mrs. Maloney. My good friend down there at the other end, Mr. Tierney.

Mr. TIERNEY. Thank you, Mr. Chairman. Once again I thank you for holding hearings that are both relevant and important to our country.

Mr. BURTON. Before you start I want to thank you and your colleagues from Massachusetts for being so hospitable to us when we were up there recently.

Mr. TIERNEY. We were happy to do it. That is just one of the topics that we dealt with recently under your leadership in dealing with the FBI and its culture and conduct and the importance of making sure that agency is in fact protecting the interest of the American people and not working against them.

Similarly here you've shown some great leadership in bringing this issue to the forefront of the American public's consciousness. Everywhere we've seen an increase in the number of incidents of autism, and my community is no different than any others. We've seen a tremendous increase, oftentimes concentrated in very particular areas, inexplicably so. While that awareness has led to a great community response, and we have many people that have been working on this issue trying to support the families that have to care for people with autism, making sure that centers are established and facilities are available and people are there to work with the families and with the children, and the children, in particular as the children get older, in dealing with the situation of what happens with their future, that's not enough. Obviously we have an obligation to try and find out as a government, encourage and support the scientific research and try to find out what is the cause, must determine that, to educate families so that the research is available to deal with autism within their family and to find either a cure or some way to prevent autism from impacting us in the extent that it has. The resources to do this have to match the proportion of the situation. I'm not sure at all that they do.

And I think, Mr. Chairman, that you're right to raise that question, where have we been on this issue, are we projecting forward enough so that we give it the attention that it needs? Are we doing the right kinds of studies and has our government been doing historically what it needs to do to address these situations and will it be equipped to move forward as we look into the future? I think these are all important questions. This is obviously a growing concern to many communities.

For those of us that won't be able to stay for the whole hearing I want to thank our witnesses for their written testimony, which will be reviewed and which will inform us, I'm sure, in the direction we take.

I want to close just again, Mr. Chairman, by thanking you for your hard work in this area. I know it's a great personal concern to you. I think that you've moved beyond your own personal concern to embrace the concern that it has for many people across this county, and I thank you for that.

Mr. BURTON. Thank you, Mr. Tierney. Before you leave, at the end of my opening statement I was going to show two clips, but I'd like for you to see them before you leave. It will just take a few minutes.

I'd like for you to start off by showing the clip of what happens to brain tissue when it comes in contact with just a minute amount of mercury. Can you start with that one? Then I want you to show a brief tape showing what happens to a child who becomes autistic.

[Tape played.]

Mr. BURTON. Now that was a very low level of mercury that was introduced into that study. And we continue to inject or we have been continuing to inject our children with thimerosal, which does contain mercury. I don't know how anybody who could watch that and know that has validity could doubt that there's a very strong possibility that has had a debilitating impact not only on children but on senior citizens. Scientists believe, as was stated in that show, that it's a contributing factor to Alzheimer's, which has grown dramatically in recent years.

With that I want to show you, because a lot of people don't know before I make my opening statement, I want you to see what happens to a child who becomes autistic. I want you to bear in mind why I feel so strongly about this, because my grandson was a normal child and 2 days after he got nine shots in 1 day, several of which contained thimerosal, mercury, 40 some times the amount that was tolerable in an adult, he started exactly like this child. This is what parents are going through all across this country and they have no recourse. The Vaccine Injury Compensation Fund has a 3-year statute of limitations. If they don't know within that 3-year period that their child may have been affected by these vaccines, they're out of luck, and they have no place to go but the courts. And the language that my colleagues talked about that was put in the homeland security bill blocks them from ever getting restitution. And those people, some are selling their homes, they're spending their life savings, working day and night trying to take care of their kids, and it's just wrong, and our government has to 'fess up to this. And if the pharmaceutical companies are responsible, then some way they have to aid in the compensation of these people, either through additional moneys going into the victims' Vaccine Injury Compensation Fund or some other way. And the Vaccine Injury Compensation Fund needs to be revisited very soon so that these people have access to it. To leave them high and dry is criminal, in my opinion.

Now I want you to see what these parents are going through with these kids.

[Tape played.]

Mr. BURTON. I could let you watch more of that but I think you get the general idea. Now my grandson and thousands of children across this country were normal kids and they got vaccinated with multiple vaccines. And mercury in the brain has a cumulative effect; all scientists will tell you that it doesn't wash out easily. It gets in the fatty tissues and it stays there so it has a cumulative effect. And yet we continue to get reports that say there's no scientific evidence that mercury causes autism. They don't say it doesn't, they say we can't conclusively prove that mercury causes autism. They don't say it doesn't.

I was on television today, on CNN, and they had a scientist who incidentally has a 9-year-old child who's autistic. She said that there's no scientific evidence that mercury in vaccines cause autism. And I said, can you categorically say that mercury does not in any way cause autism? And she jumped all over the table trying to say, well, you know there's no studies that show it and everything, but she would not say and I have yet to find any scientist who will say that there's no doubt, no doubt, that the mercury in vaccines does not contribute to autism. Now, they'll say there's no scientific evidence, there's no studies or anything that proves that yet. But turn that around, there are no studies that disprove it either. And so they're skirting the issue.

Now, the pharmaceutical companies are involved in a great deal of research, and I think that's good, and vaccines are important. They've given us the highest quality of health of any country in the history of mankind. And I am for vaccines, but they need to be properly tested. We had the Rotoshield virus that affected children in their stomachs. And we had an advisory committee that tested the Rotoshield vaccine and they said that it was ready to go on the market. There were several people who dissented in that even in that advisory committee. But they put the Rotoshield vaccine on the market and a couple of children died, several were injured, several had to have surgery. So they took it off the market in about 11 months.

The guy who headed that advisory committee had a stock in a company that was making the Rotoshield virus vaccine. Shouldn't have done it. He had a tainted point of view. But nevertheless he did. Now, I asked the FDA how many times they do not agree with the findings and accept the findings of the advisory committees, because that's all they are, are advisory committees. Do you know how many times? 100 percent. 100 percent of the time they accept those findings and go ahead with it. So we may have some conflicts of interest here that need to be explored.

Now you may say, well, that's subjective. You're not really sure about that. What about the homeland security bill? We have a class action suit, and I'm no friend of the trial attorneys, but we have a class action lawsuit with hundreds of families that are suing because they think their children are being damaged by mercury in vaccines and our committee wrote most of that bill. We were the committee of jurisdiction, primary jurisdiction. We should have been notified of any change in the bill because we wrote most of it, but what happened? The leadership stuck in at the last minute under the cover of darkness the amendment that we've talked about today. I support my leadership, I think they're great. I think they've done an outstanding job. But that should never have happened because it cuts off the access of a lot of families who have had damaged children from any source of compensation for their child's injury, and it's just wrong and it was designed to protect the pharmaceutical industry, and that's not right.

Now, you say, well, if it was designed to protect the pharmaceutical industry and it was stuck in there, nobody really knows who did it, you can't find anybody in that gang that got it done that's going to own up to that, then there must be some concern that the suit might be successful. And so they're throwing those kids out in the cold and their parents who are mortgaging their homes and losing their life savings trying to take care of a child like that so they can protect their company. Now, I want to tell you, I want to protect the pharmaceutical companies. I voted for the Vaccine Injury Compensation Fund, which was to put money out of each shot that was given to people into the fund so that if there was damage they could go to that fund and get restitution, get some help for their kids or whoever was damaged by the vaccine. But it's not a nonadversarial program. We've got people who have waited 10 years. And then they've been threatened by the Justice Department in some cases if they say anything about the problems and the roadblocks they've run into. They'll extend that time before they get compensation for another year or two or three, and they need the money desperately for their kids. Is that the way government should operate?

I think not.

Now, if we have to say to the pharmaceutical companies, OK, we are going to extend the Vaccine Injury Compensation Fund for a longer period of time so that the fund parents have access to it, who missed the boat, then so be it. If we have to say to the pharmaceutical companies that you're going to have to put a little bit more money out of each vaccination that's given into the Vaccine Injury Compensation Fund so these kids are protected, then so be it.

If they would do that, I'd get off their back and our committee would get off their back and the Congress would get off their back.

But, no, what do they do under the cover of darkness? They try to block every attempt for these parents to get restitution, and that is wrong. It's wrong for our government to participate in that, and it's wrong for the pharmaceutical companies to participate in that. It's wrong to throw those people out in the cold who have been damaged. And it's not just a few; it used to be one in 10,000, and now it's one in more than 250 kids that are being damaged in this country that are autistic.

Now, those kids are going to grow up. They aren't going to die. It's not like a lot of diseases where they get infected and they drop dead. They're going to live to be 50, 60 years old. Now, who do you think's going to take care of them? It's going to be us, all of us, the taxpayers, and it's going to cost, I think, as you said, Mrs. Maloney, trillions of dollars.

So we can't let the pharmaceutical companies and our government cover this mess up today, because it ain't going to go away, and it's going to cost the taxpayers trillions more if we wait around on it. And for our FDA and HHS and the health agencies to continue to hide behind this facade that there have been studies that conclusively prove otherwise is just wrong, too, because not one of them is going to tell you that there's no doubt whatsoever that mercury in vaccine does not cause or contribute to autism; and the same thing is true with the MMR vaccine. We need to have conclusive evidence, and that means, don't say we can't prove that it causes it.

Turn that argument around. We can't prove that it doesn't, so we're going to study it and we're going to find out. And you in the health field, you who run our health agencies in this country who are sitting here today, you have an obligation to these kids that you just saw there, to make sure that these studies are complete, thorough, so that everybody knows that we have all the facts. And you don't have that.

And when you come up to testify today from HHS, I want you to tell me that you are absolutely sure 1,000 percent that the mercury in the vaccines has no impact whatsoever on autism. If any of you will tell me that, I want you to prove it to me, and if you can't, then, damn it, get on with doing another study.

I have been fighting this battle for 3 years, as has my committee, and we are tired, but we're not nearly as tired as all these families that are watching their kids grow up, banging on the walls and having chronic diarrhea and constipation and other things. You shouldn't let that happen, and you should get to the bottom of it.

Now, I know you people over at HHS and CDC don't like me much, and I really don't care. I care about these kids, and I care about my grandson; and I'm not going to be chairman anymore, and a lot of you people think, well, he's not going to be chairman anymore so we'll have him off us. You will not have me off your back. I'm going to be a subcommittee chairman and I'm going to make absolutely sure that I'm going to have under my control the investigations of our health agencies because of this very issue. And so I'm not going to go away and neither is this committee, and we are going to continue. And the new chairman, I'm going to talk to him when necessary about subpoenaing you back before the subcommittee to talk about this issue.

So, please, for the sake of these kids, and for your own sakes if necessary, study this thing thoroughly. Study the thiomersal in the vaccines. If you want to protect the pharmaceutical companies because you have been getting, indirectly or directly, money for grants and stuff for scientific research, that's OK. I don't like it, but that's OK. Just make sure that the Vaccine Injury Compensation Fund works and that the parents who have had damaged kids will be able to go to that compensation fund and get restitution without having to mortgage their homes to pay for legal fees that aren't paid until the end, because they can't do it. And there's a lot of lawyers that won't even take those cases because they want to get their money as they spend their time.

So I think I have said enough. I'm just telling you, I feel so strongly about this because I've seen these mothers and these fathers come forward with tears in their eyes, crying, saying, we've got this terrible problem and we have nowhere to go, nowhere to turn; and our kids were damaged, and they changed right after they got these vaccines. And it ain't right, it's just not right.

So I have said enough. Our first witness, and I'm sorry I didn't read all of the opening statement today. I know my staff worked real hard on it.

First panel is Dr. Baskin, Dr. Geier and Dr. Spitzer, and we'd appreciate it if you'd approach the witness table and stand to be sworn.

[Witnesses sworn.]

Mr. BURTON. Dr. Baskin, would you like to start with an opening statement?

STATEMENTS OF DAVID BASKIN, M.D., PROFESSOR OF NEUROLOGICAL SURGERY, BAYLOR COLLEGE OF MEDICINE, HOUSTON, TX; MARK GEIER, M.D., PH.D., GENETIC CONSULTANTS OF MARYLAND, BETHESDA, MD; AND WALTER SPITZER, M.D., M.P.H., F.R.C.P.C., EMERITUS PROFESSOR OF EPIDEMIOLOGY, McGILL UNIVERSITY, MONTREAL, CANADA

Dr. BASKIN. Yes, sir.

Mr. Chairman, distinguished members of the committee, colleagues, ladies and gentlemen, my name is David Baskin. I'm a professor of neurosurgery and anesthesiology at Baylor College of Medicine. I'm a neurosurgeon. I do complex spine and brain surgery, about 350 cases a year.

I have also been involved in research, looking at ways to protect the nervous system from damage and to reverse damage, for over 20 years, and have over $1 million in Federal funding, both from NIH and BIA, as well as State funding and private funding from foundations, to look at a variety of issues in terms of brain damage. In fact, our group was involved in the discovery of the drug that could reverse paralysis in spinal cord injury, which has now become the standard of care. So I've been working in this area for over 20 years.

I also serve on scientific advisory boards for NIH, as well as the Cure Autism Now Foundation, the largest private funder of autism research in this country, which funds over $7 million a year.

Now, as you said, Mr. Chairman, autism is exploding. This is a recent cover of Time magazine talking about the fact that over— now, it looks like one in 150 children suffer from some form of autism.

What is autism? It's a lifelong brain disorder with very severe problems communicating, responding to surroundings and forming relationships. Most of these children, as you say, will grow up and will require lifelong care and cannot live independently. Horrible fact, over one-half will never speak. Many of them will never be even able to look at their parents and tell them they love them.

It's worse than Alzheimer's disease. There's been a tremendous focus on Alzheimer's disease, but these children never had a chance to enjoy life before they lost it.

Let's look at some medical definitions. What's a preservative? I looked it up in Stedman's medical dictionary, and it says a preservative is a substance added to a product for the purpose of inhibiting or destroying microorganisms.

What's a poison? A poison is a substance that, when injected in a relatively small amount, causes damage to structures or disturbance of function.

Now, while there's going to be quite a bit of debate this afternoon over dosages, make no mistake, there is the intent to put a preservative in these vaccines to prevent the growth of microorganisms that has gone awry, because the preservative that was used ended up being a poison.

There is no debate in the scientific literature that mercury is a potent neurotoxin. We've known that since the late 1890's. The debate only comes to degree and extent and that sort of thing. So I don't think in the course of your deliberations today you should confuse that fact. We are talking about a known poison, neurotoxin, that's been added to these vaccines with the initial idea that it would function as a preservative.

Mercury has a long history of medical misadventures. In 1890, ethyl mercury was synthesized in London, and it soon became a popular treatment for syphilis. The saying went, "A night with Venus and a lifetime with mercury." In fact, in 1927, the Nobel prize was awarded because it was felt you could improve outcome by adding treatment with mercury. Many of these patients developed serious neurological disorders, but it was thought initially this was due to the syphilis, when it turns out that a lot of these cases, retrospectively reviewed, had evidence of mercury toxicity.

Thimerosal was placed in vaccines in the late 1930's; and guess what: Three years later Tanner first described the syndrome of autism—never ever been described before in the medical literature. The neurotoxicity of mercury has been very well established in terms of brain injuries since the 1960's, as you'll see.

In 1956 and 1960, there were massive outbreaks of mercury poisoning in Iraq, and the reason this happened was that ethyl mercury was used as a fungicide. The grain was treated with this fungicide, the idea being that you could plant this grain, it would grow, the crops would flourish. But I would imagine, because of poverty, a lot of this grain was just taken and made right into bread and people ate it. So they ate these doses of mercury. And there were hundreds of cases, both in Iraq and then there was a similar outbreak in China.

A number of these cases just had really severe, horrible brain damage, but what came out of this work, there was a much more mild syndrome with developmental delays and neurodevelopmental disorders, problems with language, problems with communication. Some of the descriptions of these kids looked just like your videotape. So there was a—pretty early in the 1960's it was known there was a direct relationship of the dose of mercury received and the severity of the injury, and as early as the late 1960's, the scientific literature said the fetal and infant brain is clearly more sensitive than the adult brain.

The brain damage in these cases was studied, and it's interesting that the type of brain damage seen was the loss of the Purkinje cells, which are cells in the cerebellum, and the loss of the cortical column, which is the part of our brain that is involved in complex thought. And guess what: At the recent meeting for autism research at the Society for Neuroscience, this exact same histopathology has been described in autism.

There were other outbreaks elsewhere, so we've known about this scientifically for a long time. There is no debate that this is a toxin that causes brain injury.

Now, there was a study trying to look at lower-dose exposures conducted in the Faroe Islands beginning in 1987, and what this did was it looked at 1,000 children and it followed them from birth to age 7. It tested them very specifically for neurodevelopmental disorders. It measured blood levels of mercury in the umbilical cord, and it found an association between very low doses of mercury and neurodevelopmental disorders just like autism, and found that mercury here actually wasn't as predictive as the blood levels, which is the gold standard.

The Environmental Protection Agency established, as a result of primarily these horrible problems in Iraq, a standard for what was a maximum safe level of ingestion of mercury, which was 0.1 microgram per kilogram per day, and they called this, “a level of daily exposure that was likely to be without an appreciable risk.”

They based this on 81 children in Iraq. They looked at symptoms very much like autism—problems talking, problems with mental cognition, problems with walking; and as recently as 2000, our National Research Council reviewed this data and supported these limits, said these are the right limits to use not only based on the Iraqi experience, but also based on the Faroe Islands experience.

Let’s look at what the children actually received. This can be a source of debate. There are a lot of different ways to calculate these numbers, but what I have done here is simply taken the FDA’s numbers as they prevented them published by Leslie Ball in 2001; and if you look at the various numbers, you see that a child, by 6 months, receives somewhere between one-and-a-half to three times the maximum safe EPA dose of mercury.

If you take into account that mercury is preferentially taken up into the brain at five times the concentration, these kids are getting somewhere around 12 to 15 times the maximum dose, and that is the most conservative estimate.

Making lots of assumptions that many scientists wouldn’t agree with, they’re overdosed. Yet the last formal review by the FDA was in 1976, and they said, “No dangerous quantity of mercury is likely to be received from biological products in a lifetime.” Mind you, this is 16 years after the experience in Iraq with all the mercury poisoning, and also the outbreak in China.

Dr. Ball in 2001 said, “Reassessment of the risk is appropriate.” I think that was a nice thing to say, but I think that really—consistent with prior testimony before this committee, I think there is a concern that perhaps the FDA was asleep at the switch for decades, as was stated in an internal e-mail, that it really does only take eighth-grade math to see that they’re beyond the maximum safe levels.

The pity about this is thimerosal is not an essential component for vaccine. The argument with thimerosal is not an antivaccine argument. Vaccines are wonderful. They’re here to stay. They save lives. The argument is that you don’t need to put a toxic poison in them in order to deliver them.

But it’s worse. The incidence of autism is increasing, and we don’t know why. As you said, nobody can explain this.

There are many other sources of mercury exposure in the environment; so that if we’re going to inject our kids with a neurotoxin, and they’re already being exposed to a certain amount of mercury, this just adds insult to injury.

We clearly know infants’ brains are more sensitive. We know the blood brain barrier, the barrier to drugs between the blood and the brain, is virtually gone in infants. We know there is probably at least a five-times preferential uptake into the brain.

And we know about lead. You know, lead has been around for a long time. In one of the NIH study sections that I served on, there was a proposal to study lead and juvenile delinquency rate, and the consensus was, why do we need another study to know that lead exposure in infancy can relate to juvenile delinquency rate in adults; we already know this is the case. This is accepted science. So the idea that a metal can cause a very specific brain injury has been around a long time.

I'm going to turn my attention a moment to the article that was published by Dr. Pichichero and his colleagues in Lancet in November 2002 since this was just referred to.

[The information referred to follows:]

34

Mercury concentrations and metabolism in infants receiving vaccines containing thiomersal: a descriptive study

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Summary

Background Thiomersal is a preservative containing small amounts of ethylmercury that is used in routine vaccines for infants and children. The effect of vaccines containing thiomersal on concentrations of mercury in infants' blood has not been extensively assessed, and the metabolism of ethylmercury in infants is unknown. We aimed to measure concentrations of mercury in blood, urine, and stools of infants who received such vaccines.

Methods 40 full-term infants aged 6 months and younger were given vaccines that contained thiomersal (diptheria-tetanus-acellular pertussis vaccine, hepatitis B vaccine, and in some children *Haemophilus influenzae* type b vaccine). 21 control infants received thiomersal-free vaccines. We obtained samples of blood, urine, and stools 3-28 days after vaccination. Total mercury (organic and inorganic) in the samples was measured by cold vapour atomic absorption.

Findings Mean mercury doses in infants exposed to thiomersal were 45·6 μg (range 37·5-62·5) for 2-month-olds and 111·3 μg (range 87·5-175·0) for 6-month-olds. Blood mercury in thiomersal-exposed 2-month-olds ranged from less than 3·75 to 20·55 nmol/L (parts per billion); in 6-month-olds all values were lower than 7·50 nmol/L. Only one of 15 blood samples from controls contained quantifiable mercury. Concentrations of mercury were low in urine after vaccination but were high in stools of thiomersal-exposed 2-month-olds (mean 82 ng/g dry weight) and in 6-month-olds (mean 58 ng/g dry weight). Estimated blood half-life of ethylmercury was 7 days (95% CI 4-10 days).

Interpretation Administration of vaccines containing thiomersal does not seem to raise blood concentrations of mercury above safe values in infants. Ethylmercury seems to be eliminated from blood rapidly via the stools after parenteral administration of thiomersal in vaccines.

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Introduction

Thiomersal is a preservative used in vaccines routinely administered to infants and children. Its antimicrobial activity is due to small amounts of ethylmercury; the usual dose of paediatric vaccine contains 12·5-25 μg of mercury.[1-3] When vaccines containing thiomersal are administered in the recommended doses, allergic reactions have been rarely noted, but no other harmful effects have been reported.[4] Massive overdoses from inappropriate use of products containing thiomersal have resulted in toxic effects.[5-9]

Mercury occurs in three forms: the metallic element, inorganic salts, and organic compounds (eg, methylmercury, ethylmercury, and phenylmercury). The toxicity of mercury is complex and dependent on the form of mercury, route of entry, dosage, and age at exposure. Mercury is present in the environment in inorganic and organic forms, and everyone is exposed to small amounts.[10,11] The main route of environmental exposure to organic mercury is consumption of predatory fish, especially shark and swordfish. A 6-ounce can of tuna contains 2-127 μg (average 17 μg) of mercury.[12] Freshwater fish (eg, walleye, pike, muskie, and bass) can also contain high concentrations of mercury.

Most of the toxic effects of organic mercury compounds take place in the central nervous system, although the kidneys and immune system can also be affected.[10,11,13] Organic mercury readily crosses the blood-brain barrier, and fetuses are more sensitive to mercury exposure than are children or adults. Data about potential differences in toxicity between ethylmercury and methylmercury are few. Both are associated with neurotoxicity in high doses; in-utero poisoning with methylmercury causes problems that are similar to cerebral palsy. Findings about the effect of low-dose methylmercury exposure on neurodevelopment in infants are contradictory.[14,15] In-utero exposure could be related to subtle neurodevelopmental effects (eg, on attention, language, and memory) that can be detected by sophisticated neuropsychometric tests-- although the conclusion is confounded by concomitant ingestion of polychlorinated biphenyls in the patients investigated.[14,15]

No toxic effects of low-dose exposure to thiomersal in children have been reported.[3] The effect of the small amounts of mercury contained in vaccines on concentrations of mercury in infants' blood has not been extensively assessed, and the metabolism of ethylmercury in infants is unknown. We aimed to assess concentrations of mercury in full-term infants after administration of routine vaccinations according to the schedule used in the USA, and to obtain additional information about the presence of mercury at other body sites including urine and stool. Samples of hair and breast milk were also obtained from some mothers of infants participating in the study.

Methods

Study populations

We studied two groups of full-term infants who differed in their history of exposure to vaccines containing thiomersal. Infants in the exposure group were recruited at the Elmwood Pediatric Group, a large paediatric practice in Rochester, NY, USA, where vaccinations with thiomersal preservative were routinely given. 20 infants aged 2 months and 20 aged 6 months were studied at this practice to obtain information about the range of total thiomersal exposures likely to take place during infancy. The control group consisted of 21 infants who did not receive vaccines containing thiomersal and were recruited from the National Naval Medical Center, Bethesda, MD. All the infants were recruited during routine well-child examination and vaccination visits by the investigators (between November, 1999 and October, 2000). Written informed consent was obtained from parents for all procedures.

Vaccines

Vaccines containing thiomersal that were given to infants in the exposure group included Tripedia (diphtheria-tetanus-acellular pertussis vaccine; Aventis Pasteur, Swiftwater, PA; 0·01% thiomersal, 25 µg mercury per dose) Engerix (hepatitis B vaccine; GlaxoSmithKline, Rixensart, Belgium; 0·005% thiomersal, 12·5 µg mercury per dose), and in some children HibTITER (*Haemophilus influenzae* type b conjugate vaccine, Wyeth-Lederle, Pearl River, NY, USA; 0·01% thiomersal, 25 µg mercury per dose). Vaccines administered to the control group included Infanix (diptheria-tetanus-acellular pertussis vaccine; GlaxoSmithKline, Rixensart, Belgium), Recombivax HB (hepatitis B vaccine; Merck, West Point, PA, USA), and ActHIB (*Haemophilus influenzae* b conjugate vaccine, Aventis Pasteur, Swiftwater, PA, USA).

Procedures

We obtained vaccination histories--including type of vaccine, manufacturer, lot number, and dates of administration--from the medical records. In the exposure group, we obtained samples of heparinised whole blood, stool, and urine, during a visit 3-28 days after vaccination. Blood and urine were kept at 4°C, and stools were frozen until assessment. Urine was sampled by use of a urine bag at the clinic, and stool was taken from a diaper (nappy) provided by the parent. Whole blood and urine were obtained from the control children. At both sites, we obtained at least 50 hairs from the mother by cutting at the base near the scalp in the occipital area, to assess potential transplacental exposure of infants to mercury. Additionally, several samples of breastmilk or formula were obtained from mothers of infants at Elmwood Pediatric Group, as well as stool samples from a few infants who were not exposed to thiomersal.
We measured total mercury in all samples (and inorganic mercury in stool samples) by cold vapour atomic absorption as previously described.[16,17] The limit of reliable quantitation in this assay ranged between 7·50 nmol/L and 2·50 nmol/L, dependant on sample volume.

Population pharmacokinetic calculations

To estimate the half-life of thiomersal mercury in the blood, we developed a prediction model for the expected concentrations of mercury in blood for half-lives of mercury ranging from 1 day to 45 days, on the basis of bodyweight of the infant, the doses of thiomersal administered, and the times between the individual doses of thiomersal and when the blood was obtained. To do these calculations, we assumed that 5% of the mercury dose was distributed to blood,[7] that blood volume represented about 8% of the infant's bodyweight, and that elimination of mercury from blood followed a single-compartment model with first-order kinetics. For each possible half-life between 1 and 45 days, we then calculated the difference between the predicted and actual recorded concentrations in blood for each infant. Only measurements within the range of reliable quantitation were used in these calculations.

The best estimate of the blood half-life of mercury was judged to be the hypothetical half-life, which resulted in the smallest difference between predicted and observed values. We constructed a 95% CI based on a likelihood ratio for this estimate with the assumption that errors from the decay model were independent, additive, and normally distributed. The 95% confidence limits were the points where the curve crossed the minimum sum of squares multiplied by $1+{}^2(1)/(n-1)$ where n is the number of data points and ${}^2(1)$ is the upper 5% point of the ^{2} distribution on one degree of freedom.

Statistical analysis
Because this was a descriptive study we did no formal calculations for sample size. Student's *t* test and Fisher's exact test were used to compare results for the exposure and control group, with p0·05 judged to be significant.

Role of the funding source
The sponsors of the study approved the study design but had no other involvement in the in study design, data collection, data analysis, data interpretation, or writing of the report.

Results
61 infants were enrolled in this study (table). Among infants aged 2 months in the exposure group, samples were taken from eight within 7 days of vaccination, from five between 8 and 14 days after vaccination, and from seven between 15 and 21 days after vaccination. Among 6-month-old infants in the exposure group, samples were taken from seven between 4 and 7 days after vaccination, from eight between 8 and 14 days after vaccination, and from five between 15 and 27 days after vaccination. Samples were obtained from infants in the control group at regularly scheduled visits at 2 or 6 months of age. All children remained healthy throughout the study and during 24-36 months of follow-up.

	Infants aged 2 months		**Infants aged 6 months**	
	Thiomersal-exposed (n=20)	Controls (n=11)	Thiomersal-exposed (n=20)	Controls (n=10)
Bodyweight (kg)				
Mean (range)	5·3 (4·0-6·4)	NR	8·1 (6·7-10·6)	NR
Total mercury exposure (µg)*				
Mean (range)	45·6 (37·5-62·5)	0	111·3 (87·5-175·0)	0
Blood mercury (nmol/L)				
Number of samples tested	17	8	16	7
Number with mercury in range	12	1	9	0
Mean (SD)†	8·20 (4·85)	4·90	5·15 (1·20)	..
Median (IQR)†	6·15 (4·60-10·85)	4·90	5·30 (4·55-6·10)	..
Range†	4·50-20·55	..	2·85-6·90	..
Urinary mercury (nmol/L)				
Number of samples tested	12	6	15	8
Number with mercury in range	1	0	3	0
Mean (SD)†	3·8‡	..	5·75 (1·05)	..
Median (range)†	3·8‡	..	6·2 (4·55-6·45)	..
Stool mercury (ng/g dry weight)				

Number of samples tested	12	NT	10	NT
Number with mercury in range	12	..	10	..
Mean (SD)†	81·8 (40·3)	..	58·3 (21·2)	..
Median (IQR)†	83·5 (47·0-121·3)	..	58·0 (42·0-68·5)	..
Range†	23·0-141·0	..	29·0-102·0	..

NR=Not recorded. NT=not tested. *Via vaccination. †All calculations done only with samples within range of accurate quantitation. ‡Only one value so SD and range are not applicable.

Concentrations of mercury in blood, urine, and stool of infants who received vaccines containing thiomersal and those who did not

Sufficient volumes of blood (1 mL) for the measurement of mercury by the atomic absorption technique were obtained from 17 infants aged 2 months and 16 aged 6 months in the exposure group. Mercury concentrations were below the range of reliable quantitation in five of 17 blood samples from 2-month-olds, and seven of 16 blood samples from 6-month olds (p=0·48). The mean concentration of blood mercury in samples with quantifiable mercury was higher in 2-month-olds than in 6-month olds (difference 3·05 nmol/L, 95% CI 0·03-1·24, p=0·06), but was low in both these groups (table). Sufficient blood volumes for measurement of mercury were obtained from 15 infants in the control group, including eight aged 2 months and seven aged 6 months. Blood mercury was below the level of reliable quantitation in seven of the eight samples from the 2-month-olds and in all seven samples from 6-month-olds. The only detectable value from the control group was 4·65 nmol/L.

Overall, mercury concentrations were below the range of quantitation in 12 of 33 samples from thiomersal-exposed infants and in 14 of 15 unexposed infants (p=0·04). The highest level of blood mercury detected in any infant in this study was 20·55 nmol/L, which was measured 5 days after vaccination in a 2-month-old infant weighing 5·3 kg, who had received vaccines (Tripedia and Engerix B) containing a total dose of 37·5 μg mercury. The relation between time between vaccination and sampling and the concentration of mercury in the blood in the exposed group is shown in figure 1. Although mercury concentrations were uniformly low, the highest levels were recorded soon after vaccination.

Figure 1: **Blood mercury concentrations in infants aged 2 months (diamonds) and 6 months (squares) by time of sampling**

Filled symbols represent measured values and open symbols represent samples at the limit of quantitation, either 7·50 nmol/L, 3·75 nmol/L, or 2·5 nmol/L, dependent on sample volume.

Mercury was undetectable in most of the urine samples from the infants in this study. Only one of 12 urine samples from 2-month-olds, and three of 15 from 6-month-olds in the exposure group, and none of the 14 samples from the controls, contained detectable mercury. The highest concentration of urinary mercury detected was 6·45 nmol/L, in a 6-month old infant in the exposure group (table).

Stool samples were collected from infants in the exposure group. All of the stool samples from infants who received thiomersal-containing vaccines had detectable mercury, with concentrations in stools from 2-month-old infants slightly higher than those in 6-month-olds (p=0·098, table). As expected, most of the mercury in stools was inorganic. Stool samples were not obtained from control infants; therefore, to determine whether dietary intake could contribute to the mercury content of stools, we also obtained samples from nine infants at Elmwood Pediatric Group who were age-matched with the infants in the exposure group and were not exposed to vaccines containing thiomersal. The mean mercury concentration in the stools of these infants was 22 ng/g dry weight (SD 16), which was significantly lower (p=0·002) than the mean of the samples collected from thiomersal-exposed infants.

Amounts of mercury measured in maternal hair are shown in figure 2. The mean concentration of hair mercury in mothers of the exposure group was 0·45 μg/g hair, whereas the mean amount in mothers of the control infants was 0·32 μg/g (p=0·22). Eight mothers of infants in the 6-month-old cohort provided breast milk samples. Concentrations of mercury in these samples were low (mean=0·30 μg/g, range 0·24-0·42 μg/g).

Figure 2: **Mercury concentrations in hair from mothers of infants**

Bar represents mean concentration of mercury in maternal hair.

We estimated the half-life of mercury in blood after vaccination to be 7 days, since this result gave the smallest difference between the expected and recorded (measured) concentration (figure 3). The 95% CI around this estimate was 4-10 days. The half-life estimate was very similar when only measurements in 2-month-olds (7 days, 95% CI 4-11) or 6-month-olds (5 days, 3-9) were included, suggesting that the rate of elimination of thiomersal mercury from blood was similar in both age-groups.

Figure 3: **Estimated blood half-life of mercury in infants who were exposed to thiomersal**
Lines represent sum of square of differences between observed concentrations of blood mercury (nmol/L) and those predicted for every individual infant on the basis of bodyweight and time of sampling, with a series of hypothetical half-lives shown on x axis. Arrow shows point with lowest value for squared difference, indicating best estimate for serum half-life.

Discussion

We have shown that very low concentrations of blood mercury can be detected in infants aged 2-6 months who have been given vaccines containing thiomersal. However, no children had a concentration of blood mercury exceeding 29 nmol/L (parts per billion), which is the concentration thought to be safe in cord blood;[18] this value was set at ten times below the lower 95% CI limit of the minimal cord blood concentration associated with an increase in the prevalence of abnormal scores on cognitive function tests in children. Blood mercury concentrations indicate concentrations in organs well.[18]

Although our study was not designed as a formal assessment of the pharmacokinetics of mercury, we did obtain samples of blood at various time points after exposure. Assessment of these samples suggested that the blood half-life of ethylmercury in infants might differ from the 40-50 day half-life of methylmercury (range 20-70 days) in adults and breastfeeding infants.[10,19] The concentrations of blood mercury 2-3 weeks after vaccination noted in our study were not consistent with such a long half-life, but suggested a half-life of less than 10 days. However, this conclusion is based on several assumptions and a very simple model, and does not take into account the fact that at least some of the mercury detected in the blood of the infants in this study is likely to have been derived from exposures other than vaccination. Because of the short period between vaccination and sampling, the findings of Strajich and colleagues[20] could be consistent with either a 6-day or 40-day half-life, but are otherwise consistent with the assumptions made in our model. Because we expected a 45-day half-life on the basis of methylmercury pharmacokinetics, the first blood samples were obtained 3 days after vaccination. Blood samples taken in the first 72 hours after vaccination, stool samples obtained every 24 h, and samples from premature newborn babies (weighing 2000 g) given a birth dose of hepatitis B vaccine would have helped us to reach stronger conclusions. Thus, additional studies of the pharmacology of thiomersal in infants are underway.

At the times tested after vaccination, mercury excretion in urine in our study population was low. By contrast, concentrations of mercury in stool were high, and combined with the finding that stool mercury concentrations in infants who were not exposed to thiomersal were significantly lower is consistent with the hypothesis that the gastrointestinal tract represents a possible mode of elimination of thiomersal mercury in infants.
Overall, the results of this study show that amounts of mercury in the blood of infants receiving vaccines formulated with thiomersal are well below concentrations potentially associated with toxic effects. Coupled with 60 years of experience with administration of thiomersal-containing vaccines, we conclude that the thiomersal in routine vaccines poses very little risk to full-term infants, but that thiomersal-containing vaccines should not be administered at birth to very low birthweight premature infants. Decisions about the elimination of thiomersal from these vaccines must balance the potential benefit of reduced exposure to mercury against the risks of decreased vaccine coverage because of higher costs, the risk of sepsis in recipients because of bacterial contamination of preservative-free formulations, and the risks of exposure to alternative preservatives that might replace thiomersal.

Conflict of interest statement
None declared.

Contributors

M Pichichero and J Treanor contributed to the study conception and design; obtained, assessed, and interpreted data; drafted and revised the manuscript; and provided statistical expertise and supervision. E Cernichiari contributed to analysis and interpretation of data, revision of the manuscript, and technical support. J Lopreiato contributed to revision of the manuscript, and obtained data.

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■Commentary

Mercury in vaccines--reassuring news

The mass media and alternative-medicine publications increasingly report that exposure to and the build-up of mercury within the body is associated with chronic ill-health, particularly conditions such as myalgic encephalitis. Mercury is widespread in the environment; it is found naturally in rocks, soils, and plants and as a contaminant in air, water, and food. The element is used a lot in the electrical industry, and in many domestic products, including paints, pesticides, fabric softeners, waxes, and polishes. Mercury is often used as a preservative in vaccines, skin creams, cosmetics, and other medications. Mercury is the major component of dental amalgams and there is a growing lobby against its use.[1] Everyone is exposed to small amounts of mercury as elemental metallic vapour from dental amalgams or organic mercury from fish, sea foods, and vaccines, or to inorganic salts from other food stuffs, water, and air. Faecal excretion is the major route of elimination of inorganic or organic mercury.

Elemental mercury from amalgams is lipid-soluble and freely passes through cell membranes.[2] By contrast, organic and inorganic mercury from the diet and other sources are charged and must be complexed with other counter-ions or low-molecular-weight sulphur compounds to pass through cell membranes. The major targets in proteins susceptible to binding of metals, including mercury, are the sulphydryl group of cysteine and the iminonitrogen of histidine. The aromatic ring nitrogens of the nucleotide bases form mercury complexes, with thymine and uracil being more reactive than cytosine, guanine, and adenine.[3,4] The most abundant single nucleophile reactant is the antioxidant glutathione, typically present at concentrations of 5 mmol/L in cells, serum, and bile.[5] Glutathione mops up ionised mercury derived from oxidation of elemental mercury and from organic and inorganic mercury. There may be an inverse relation between the concentration of intracellular glutathione and mercury toxicity.[6] Once bound to glutathione, mercury can leave the cell and circulate freely in serum and lymph from where it can be deposited in other organs and tissues. Glutathione-complexed mercury is eventually eliminated via the kidney or downloaded via bile into the intestinal lumen from where it is excreted in faeces. After mercury is released from tissues, faecal excretion is the predominant route for elimination.

In this issue of *The Lancet*, Michael Pichichero and colleagues investigate mercury levels and excretion in infants receiving vaccines containing thiomersal (ethyl mercury). Little is known about the harmful effects of mercury in infants and children and at what level these effects occur. At between 12·5 and 25 mg mercury per vaccine dose, the infants may be receiving over 100 mg ethyl mercury in the first 6 months of life. Pichichero and colleagues show that the levels in blood are much lower than the prescribed limits and that much of the ethyl mercury appears to be eliminated rapidly in faeces. This study gives comforting reassurance about the safety of ethyl mercury as a preservative in childhood vaccines.
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Dr. BASKIN. This was a study of 40 infants, age 6 or younger, in which they measured blood, urine and stool mercury levels. The conclusion was that administration of that change containing mercury did not seem to raise blood concentrations of mercury above the safe values.

The data are the data, and I think, as you said, Dr. Weldon, it's good to have some data, but interpretation of data is paramount. In my residence, we teach residents and we teach young doctors how to be neurosurgeons. We spend a night a month pouring over the medical literature and make the important distinction that while the data in the papers are probably correct and true, the way you interpret the data, the way you look at that and come to a medical conclusion is often subject to interpretation; and I'm going to show you and talk to you about the fact that while the data are the data, I think the conclusions are not borne out.

First of all, I was shocked when I read this study that there was no disclosure of conflict of interest. As an NIH scientist, anytime anybody funds my research for any reason, I have to disclose the conflict of interest. Yet these authors have vaccine patents, have received numerous funding for studies by drug companies that make vaccines; and I was surprised that Lancet took it. I'm sure it's not over with. Whether or not there's a true conflict of interest, they certainly should have revealed it.

The sample size, as you said, Dr. Weldon, was small. Autism occurs in one in 150 kids. So if a child had some different tendency in their blood to absorb more mercury or have it remain in the blood longer or be more sensitive in their brain, if they only checked 40 kids, they may well not have found even one kid with a predisposition to autism. So it's a meaningless study without a larger sample size.

The sample wasn't random. They didn't take kids from different portions of the population in different areas. If there's some metabolic difference based on race or sex or where you live or other things, they wouldn't have found it. They didn't even talk about the preferential uptake of mercury into the brain, which is fivefold.

But they did find a very high stool level of mercury, and one kid had 81.3 nanograms. If you again go to the very conservative FDA data, a 50 percentile kid receives 20.7 nanograms per gram. So somehow the mercury went from the injection, ended up in a much higher level in the stool. And obviously, the mercury gets to the stool by traveling through the blood; there's no rectal administration. If you put gasoline in your car that has lead in it and somebody comes by and scrapes your tail pipe and says we have a high lead level, it got there by traveling through the system.

So what happened here is, we know the stool levels were high, but if you look at when they actually measured the blood levels, they said it was somewhere between 3 and 27 days later. The peak mercury levels after injection occur within hours or at least within the first 24 hours. So if they were drawing blood later than that, and much later than that, of course the levels weren't going to be high. But the mercury doesn't jump from the injection to the stool; it goes through the blood. At some point it was high because it was high in the stool.

And because they didn't measure the peak levels, they can't even talk about what they did, which is the pharmacal kinetics, which basically means the way the drug is metabolized; and they drew a bunch of fancy curves. You can't do a pharmacal kinetic study if you don't have the peak level. They clearly didn't have the peak level because they have high stool mercury, and they have low blood mercury—doesn't make sense.

So they described this as a descriptive study, and that's exactly what it was. It provides some interesting information, it's a start, but the interpretation is inaccurate—as what we would say in neurosurgery, "The operation was a success, but the patient died."

Let me turn to some studies that we're doing at Baylor College of Medicine. We have the opportunity to actually grow human frontal cortex cells in cell culture. So these are cells from the front part of the brain that grow in culture. We incubate these cells with thimerosal at various doses, and we use a number of very sophisticated techniques to detect cell death and cell damage.

It turns out that every cell has a program inside of it to commit suicide. The reason we have this in our bodies is, when we're babies we have webs between our fingers, but when we're born, we don't have these webs. These cells are eliminated by activating a genetic program, so there's no inflammation and there's no scar tissue.

We basically start out with many more cells than we end up with. We kind of prune ourselves into shape, and this process is called apoptosis. Well, it turns out that toxic substances, including mercury, turn on this suicide program in the brain.

Here are some pictures from our cell culture experience, and you can see the arrows pointing to those little knobs sticking off the cell. These are the cells committing the suicide program and breaking themselves into tiny little pieces with a very low dose of mercury.

Here is a slide where you see a lot of blue cells. This is a blue dye that normal cells don't take up. In order for something to turn blue, the cell has to have holes punched in their membranes. And guess what: At an extraordinarily low dose of thimerosal, most of the cells are blue. It means that this stuff grabs ahold of the membrane and punches holes into it, so that the dye can penetrate, not only into the cytoplasm but into the very center of the cell, the nucleus, where all the DNA exists.

This is a fascinating slide. The center of the cells are blue, which means there have been holes punched into the membranes so the dye gets to the center of the cell. The rest of the cell is green which is the release of an enzyme that only gets released during the suicide program. So these cells are turned on to commit suicide or go into apoptosis.

We found this to be dose- and time-dependent. We found that 101 nanograms per gram is the lowest dose we've studied, and it's toxic. And we didn't even expect this to be toxic, yet if you consider a five-times preferential uptake and you use FDA numbers, infants receive 380.5 nanograms, three times the dose that we found to be toxic to brain cells.

Don't forget, we did this in adult brain cells. Remember that infant brain cells are much more sensitive, so there's a real cause for concern.

In addition, there was discussion that there's no scientific data or evidence. I don't agree with that. At the recent International Meeting for Autism Research at the Society for Neuroscience, a number of investigators around the world are finding similar things.

At Columbia University, there's now a model in mice who were injected with low doses of thimerosal very similar to what's given in human vaccines. These mice develop neurological deficits that look like autism, and when you take their brains out and you analyze them, they have the same type of brain damage.

There's evidence that thimerosal not only binds to the proteins you saw in the cartoon, but also binds to sulfur groups which are pretty essential groups for the membrane. So this is probably how it punches holes in the membrane.

This is work at Northwestern, and the very important work that is coming out of a number of NIH-funded centers is that if you give patients thimerosal, you can take their lymphocytes and make them killer lymphocytes and trigger the onset of autoimmune disease, which also may be part of what's happening in terms of brain damage.

So science has come a long way. We've gone from caveman clubs, and now we're at ICBM missiles, and I would be very optimistic that in the next few years, Mr. Chairman, you're going to see a tremendous amount of scientific data supporting the fact that this is a horrible toxin that shouldn't ever have been in these vaccines.

Well, what can you do? What can Members of Congress do to try to make this better, to do something to improve the situation?

First of all, as a physician, I probably prescribe a pound of drugs a week and, you know, I always rely on the FDA. I don't go through and test the safety data of each drug myself; I assume it's safe.

Somewhere along the line, the process failed. Mercury is a known neurotoxin, and you know what: It's still being given today in flu vaccines, to pregnant mothers and to children. Why? It's not necessary.

So I think one thing you can do is compel the CDC and the FDA to do their jobs. Insist on properly managed accountability. Insist on conflict-of-interest disclosures. I live in Houston. We sure learned a lot from Enron, and I hope that we can avoid similar unfortunate circumstances.

I think you should consider this a problem very similar to September 11th—it's interesting, we talk about homeland security, it's a severe problem—it's chemical poisoning at home, and it's very similar. I was in a cab today, and the radio was talking about the FBI, the CIA and lack of communication that might have avoided the terrible problems of September 11th. Well, you know, the EPA knew this for a long time. All of these agencies had pieces of this data, but they don't seem to talk to each other; there doesn't seem to be any sort of coordination, very similar to the issues with homeland security.

I think another thing you can do is support the NIH. The NIH has done a great job recently trying to catch up. The NIEHS particularly, but some of the other institutes as well, has really put together first-rate scientists and first-rate programs to do this. You could help by proposing specific funds to be set aside by NIH.

NIH has something called "request for application," which means we are entertaining applications only on this subject, and then they pick the very best ones. They don't have the money to do that too often, but if you can give them a small extra pot, that would bring the very best research in this country along very quickly.

Allow science and the press and our legal system unfettered access to the issue: This is the only way the truth is going to come out, and particularly in science, if we couldn't read and critical-review each other's data, we would go nowhere. I think you have to insist on that, and by doing that, consider reversing the relevant provisions in the homeland security bill, as was discussed, and stand up for our Nation's children and their rights.

In conclusion, Plutarch said, "The mind is not a vessel to be filled but a fire to be kindled." Please do everything you can to ensure that our Nation's most valuable resource, our children, have their rights protected and can grow and flourish to their full potential. Thank you.

Mr. BURTON. Dr. Baskin, I'm going to send your presentation to everybody I possibly can, because it was so thorough, and you're to be congratulated for all that hard work. I just think you summed it up so well, and I'm going to make sure we send that over to the FDA and CDC to make sure they take a look at it.

Dr. Geier, you're recognized.

Dr. GEIER. Thank you for inviting me, Mr. Chairman and other members of this committee.

Vaccines are one of the greatest triumphs of the 20th century, resulting in the virtual eradication of most infectious diseases. Vaccine producers should be commended for their efforts, but one must openly acknowledge that, on occasion, vaccines are indeed responsible for adverse reactions.

The U.S. Government judiciously established the Vaccine Compensation Act in 1986 as one of its provisions. The Vaccine Adverse Events Reporting System data base was created. The VAERS data base has been maintained by the CDC in Atlanta, GA, since 1990, and vaccines suspected of adverse reactions are to be reported to this data base as mandated by U.S. law.

The reporting of serious adverse reactions to VAERS requires written and telephonic communication by the CDC. The CDC follows up serious adverse reactions 1 year later to determine whether the patient has recovered, and the FDA inquires into deaths reported to the VAERS data base by contacting the patient's health care provider and physician.

Despite the continuing insistence by the FDA and the CDC that the VAERS data base is subject to severe limitations, the FDA, CDC, David Geier, my son, and I analyze and publish from the VAERS data base. The VAERS data base provides a prospective about vaccine adverse reactions unobtainable by any other means, as it contains almost 200,000 adverse events, following almost 50 different vaccines resulting from more than 1 billion doses of vaccine administered in the United States.

It is biologically plausible that thimerosal, contained in vaccines, contributes to childhood neurodevelopmental delays, but there are few epidemiological analyses that study the effects of thimerosal contained in vaccines. We analyzed the incident rates of neurodevelopmental delays reported to the VAERS data base following thimerosal-containing diptheria, tetanus and acellular percusses, called DTaP, in comparison to thimerosal-free DTaP vaccines.

The CDC provided us with a number of doses manufactured and distributed each year of each type of vaccine, manufactured by each manufacturer, but in so doing, we had to agree to withhold the identities of the vaccine manufacturers because the CDC considers this information proprietary. Thus, we are prohibited from releasing data on which company makes a safer vaccine, when two or more companies make the same vaccine. We feel that it is essential that this information not be denied to doctors or patients.

The CDC and FDA also knows the number of doses of each lot manufactured. We feel it is important that this information be released so that analysis of potential so-called “hot lots” can be carried out.

This slide shows that autism and mental retardation were approximately six times statistically significantly more likely, and speech disorders were two times statistically significantly more likely following thimerosal-containing DTaP vaccines in comparison to thimerosal-free DTaP vaccines. Further, the details of our study——

Mr. WELDON. Dr. Geier, can I just interrupt you, is that published data?

Dr. GEIER. That’s been submitted and accepted with revision, but it’s not finally accepted. So it has not been published yet, but shortly we hope.

Mr. BURTON. I don’t want to interrupt you either, but I think it’s very important at this point. We talked to the health agencies about the VAERS being made public and being made available to any researchers, completely available; and you’re telling us that you still can’t that get information?

Dr. GEIER. We can—well, there are a number of problems with VAERS. First of all, VAERS is maintained by CDC in Atlanta on a data base that’s proprietary. So it’s very difficult to access. We get it accessed, and a computer programmer takes it off and puts it—makes it available so that Microsoft Access can work on it. This allows everybody to work on it.

My son has also figured out a system to put their—I think it’s seven different data bases together to make one, however, so we can get access. But you can’t just call up this site and get useful access; you get some data, but it’s not useful.

But in addition to that, in order to interpret VAERS, you need to know the denominators, you need to know how many doses were given; and we’ve been given the information of how many doses of each type of vaccine were given each year.

Additionally, in order to do these calculations, you need to know the number of doses produced by each vaccine manufacturer. We were given that with the provision that we were not allowed to tell which vaccine companies are which.

So we can do the study we did up there because, you notice, all we said is we compared the relative risk of one that contained thimerosal with a similar vaccine that didn't, didn't tell you which company. But it really hurts us to see—when we see two or three manufacturers of a particular vaccine where one is far worse than the other, that we can't publish which one is worse. And, in fact, CDC has published a paper showing, I think, a sixfold increase in serious reactions of one manufacturer versus another, and they call them manufacturer A and manufacturer B.

I think that the American public are entitled to know which manufacturer is which, so they can choose the better vaccine for their children.

Mr. BURTON. Well, I don't want to interrupt anymore of your testimony, but what I'd like to do is have you give us a list of the problems that you're having in getting this information, and we'll try to see what we can do to lift the veil of secrecy so that you can get on with your work.

Dr. GEIER. We would appreciate that very much.

The doses of mercury children were receiving from thimerosal on a given day following vaccination in comparison to the EPA, AFDR and FDA limits of exposure to mercury are summarized in the next slide, and this is similar to a slide that Dr. Baskin showed. This is what's in each one.

This calculates the risks, the amount of the excess the children received, and the way that Dr. Baskin did it was very, shall I say, "charitable" toward the production. Children actually receive from a ten- to a hundredfold excess of mercury from their childhood vaccination on the days of immunization in comparison to the guidelines. The daily dose of mercury children received was equal to or exceeded the guideline even when averaged out for 10 days following vaccination.

Further details are provided in the packet that I submitted to the committee.

The IOM analyzed the mercury dose children received at 6 months of life and averaged it over every day in a child's life, that is, 180 days, showing that the dose received by the child was only in slight excess of the EPA limits. This type of averaging makes no scientific sense. As an example, if I were given a lethal dose of mercury and my dose was averaged over my more than 50 years of life, I would not have received a dose exceeding the limits, despite the fact that I would be dead.

Realistically, children are receiving large doses of mercury at intervals that far exceed all the Federal agency guidelines and not by fivefold but by over a hundredfold.

This slide summarizes the CDC's VSD data regarding the relative risk of autism versus the mercury dose that the child received. When we saw this, we were very, very disturbed. Despite the fact that our study had shown that two populations, one population had received a vaccine with thimerosal and the other didn't, were statistically different, this is more powerful data because this is a plot of the amount of mercury that a child received versus the amount of autism, and it turns out that this plot is not linear. In fact, it goes up faster and faster with increasing mercury doses from childhood vaccines. And again, the packet I submitted has quite a bit more on these graphs.

But we did—each point in their analysis was barely significant, but the graph on the whole is very significant, and there's an interesting trick used in presenting their data. Their data had data for each of the first two points. The third point said greater than 62.5 exposure. It's kind of hard to plot greater than 62.5, and therefore, you can't do this analysis, but when we looked at it, greater than 62.5 has to be 75; there's no other possibility.

So we replotted it with 75. I mean, that's just the way the vaccines are given. And when you replot it with 75, you get a very, very good curve fit, and it's statistically significant, and it fits for several different disorders. And it's very disturbing, because this is a kinetic study. You know, if you compare two things and one is bigger than the other, well, maybe even though the statistics show it is unlikely, maybe it was chance, but when it goes up as you go up with dose, and it goes up faster and faster as you go up with more and more dose, this is very disturbing.

Also, the relative risk at the top top is 2.5. That means that of these children, who belong to the Kaiser plans, a very large segment of the autistic children were related to the thimerosal.

I mean, there are two issues. One is, can thimerosal cause autism; and another is, does it cause a significant part? I mean, maybe it only causes 1 percent of autism. This tells you that it causes a very significant part of the autism.

Now, I'd like to go into a little bit of what you asked me in the question. You asked me about the VAERS data base, and I wanted to talk to you about the VSD data base.

As described in the packet that I submitted to the committee, despite correspondence between myself and the CDC, originally dating prior to the CDC's press release to open the VSD to the public, I have not been given access to the VSD. This has been ongoing for more than 4 months, and my last proposal was more than 150 pages long.

Mr. BURTON. Let me interrupt you here just a second.

Now, the VSD, we were told by our health agencies that was going to be made available to any researcher completely; and you're telling us you're still not getting it?

Dr. GEIER. Let me go through my experience. And I gave Dr. Weldon the complete documentation of all of our exchanges.

It's available, but it's so difficult to get—I think we're in a very good position among independent researchers to ask for it, and we have little hope; and let me go over some of the barriers they've put in our way.

We've been doing this for 4 months. My last proposal was more than 150 pages long, and despite the fact that I've published approximately 30 peer-reviewed scientific studies analyzing VAERS, I still haven't been able to move beyond the first hurdle of gaining access to the VSD.

And I had a very simple solution to their question of what do you want to study. I simply said, well, let's do something really easy. Let's study whether VSD has the same kind of results as the VAERS. And you know my studies are valid because they have been peer-reviewed and published by 30 different journals, such as the Annals of Internal Medicine and Rheumatology and various other journals. So rather than going into a whole big study design, let me see if we can confirm our results with the VSD.

This didn't please them, and they required that we ask every single possible question and make various predictions, and we came up with a 150-page proposal. However, that didn't satisfy them because, first of all, they seemed to put up continually additional steps, fees and hindrances and seemed to make the realistic possibility of ever gaining actual access to the VSD remote.

Basically my understanding is, after we get them to agree to our study, which we have to describe every possible thing we want to test, then we have to go before each of the Kaiser boards in order to get their permission; and CDC does not even know what Kaiser boards will require. If we go to each Kaiser board and ask that we be able to use their Kaiser data and it's approved, then my understanding is it goes back to the CDC for approval. After the CDC approves it, then I get limited access in a little town in Maryland. This happens to be near where I live, but anybody else would have trouble, because they're going to give you like 5 minutes of access a week, so you'd have to fly in here from, say, California.

In addition, when you go there, we've been told that we can't take cell phones. We can't copy anything. We can't take any data out. We're going to be searched. All of this in the name of confidentiality when, in confidentiality, all you have to do is what VAERS does, just take the names off. And as far as validity of the studies, if the studies are valid, I'm going to submit them for peer-reviewed publication. If they're published, they're valid. I don't need them to review the validity of the studies.

Mr. BURTON. Would you ask excuse me 1 second.I think Michael Crane is here.

Mr. Crane, would you raise your hand real quickly. I'd like to talk to you after this hearing is over to find out why these impediments are put in front of these people. OK?

[Witness sworn.]

Mr. BURTON. Thank you.

Dr. GEIER. Finally, there's a constant mention of fee, and we've asked for the amount of the fee on several occasions, and we're told repeatedly there's a fee and they don't know the amount of the fee. My suspicion is no one is ever going to get that far, but we're independent and we don't have any outside support. We do this because we care about the children. So if they ask for $1 million fee, we have no granting fund to pay the fee.

Turning to another subject. I've been asked to comment on the Lancet article which measured mercury in blood, urine and stool, which was commented on by Dr. Baskin, in infants 3 to 28 days following thimerosal-containing vaccines in comparison to infants receiving thimerosal-free vaccines. The findings of low-level mercury in the blood is only indicative of measuring too late.

If they wanted to see it, they should measure 3 to 24 hours after the shot, and it does nothing to assure that these children were not exposed to potentially damaging levels of mercury. We know, in fact, these children received by injection more than 100 times the daily permissible dose of mercury, and the mercury would be more damaging in the brain than the blood.

It's almost as if they want you to read the study and think, well, I guess they didn't get any mercury. But we know they got the mercury. So why is it supposed to be reassuring that they measured later, and it's not in the blood; that means it could be in the brain. So that study, to me, has no validity. It has some interesting data, but no validity on the question of whether thimerosal causes problems.

I've also been asked to comment on the recent New England Journal of Medicine study done in Denmark, which failed to find a correlation between MMR vaccination and autism. This study attempted to compare children vaccinated with MMR to a comparable control group of children who were not vaccinated with MMR.

The author's own analysis showed that the two groups were statistically different in most respects even before being vaccinated, making the results dubious. You want to have match controls. Basically they adjusted them; I have no idea on which way to adjust. For example, if the control group and the vaccinated group differ by how their income—what their income level is, I don't know whether to raise it or lower it. Neither do they. So they just changed it in such a way that it evened out the numbers.

Even overlooking the weakness in the study design, the study would have only shown MMR to be statistically linked to autism if MMR caused a rather large proportion of all autism in the population being studied. This already was known not to be the case. HHS itself has published that there is a causal relationship between MMR and permanent brain injury.

Our study using VAERS, contained in the submitted package—this is another study we've submitted for publication—shows that MMR increases the relative risk of autism, but its contribution to autism in the whole population is relatively small since much of the autism seems to be linked to thimerosal which, of course, is not contained in the MMR vaccine.

So their study doesn't say that MMR didn't cause 10 percent of the autism. It just said it didn't cause 60 percent of the autism, and—because you'd have to have a large percentage the way they looked at it.

In conclusion, these two recent studies do little to alleviate the fact that the scientific data indicates that thimerosal in vaccines and from other sources, such as RhoGAM, a product containing thimerosal, given during pregnancy to RH-negative women, appears to cause or contribute significantly to the recent dramatic increase in the rate of autism seen in the United States.

As far as RhoGAM goes, I practice as an obstetrical geneticist. I do amniocentesis. I give RhoGAM. I was not aware that RhoGAM contained thimerosal. It no longer does, but it did for a number of years. The reason I wasn't aware of it is that I've never seen a multidose vial of RhoGAM. If it's ever been made, I have never seen it in my 22 years of practicing, and yet, they put thimerosal in it as a preservative. What the heck are they preserving?

And there are studies by clinicians who take care of these children, who find that a very high proportion of these children are born to women who are RH-negative, who had RhoGAM during the pregnancy. I see no reason in the world—if they have to put thimerosal in single-dose vials, are they afraid that they don't know how to make things sterile? Are we to assume that sterility testing is not good?

Ideally, vaccines should be killed, single antigen, highly purified and checked to determine if any of the epitopes they contain are cross-reactive with human lymphocytes. They should come in single-dose, sealed vials, so the preservatives are not necessary; and they should contain enough antigenic materials so that adjuvants are not necessary.

History has written that the fall of Rome may well have been related to lead poisoning from newly invented lead pipes. Let it not be written that our great society poisons itself with mercury preservatives. Thank you.

[The prepared statement of Dr. Geier follows:]

Vaccines
&
Neurodevelopmental Delays:
An Assessment of the Vaccine Adverse Event Reporting System (VAERS) Database
&
Other Studies

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Contents:

1. **Neurodevelopmental Disorders Following Thimerosal-Containing Vaccines (3-19)**

2. **Exposure Limits for Mercury & Childhood Prospective Assessment (20-22)**

3. **Vaccine Safety Datalink (VSD) Data (23-29)**

4. **Pediatric MMR Vaccination Safety (30-47)**

5. **VSD Access (48-52)**

Neurodevelopmental Disorders Following Thimerosal-Containing Vaccines

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Abstract

We were initially highly skeptical that differences in the concentrations of thimerosal in vaccines would have any effect on the incidence rate of neurodeveopmental disorders following childhood immunization. This study presents the first epidemiologic evidence, based upon tens of millions of doses of vaccine administered in the US that potentially associates increasing thimerosal from vaccines with neurodeveopmental disorders. Specifically, an analysis of the Vaccine Adverse Events Reporting System (VAERS) database showed statistical increases in the incidence rate of autism (Relative Risk (RR)=6.0), mental retardation (RR=6.1) and speech disorders (RR=2.2) following thimerosal-containing Diphtheria, Tetanus and acellular Pertussis (DTaP) vaccines in comparison to thimerosal-free DTaP vaccines. The male/female ratio indicated that autism (17) and speech disorders (2.3) were reported more in males than females follo~~wing thi~~merosal-containing DTaP vaccines, whereas mental retardation (1.2) was more evenly reported among male and female vaccine recipients. Controls were employed in order to determine if biases were present in the data, but none were found. It was determined that overall adverse reactions were reported in similar aged populations following thimerosal-containing DTaP (2.4 ± 3.2 years-old) and thimerosal-free DTaP (2.1 ± 2.8 years-old) vaccinations. Acute control adverse reactions such as deaths (RR=1.0), vasculitis (RR=1.2), seizures (RR=1.6), ED visits (RR = 1.4), total adverse reactions (RR=1.4) and gastroenteritis (RR=1.1) were reported similarly following thimerosal-containing and thimerosal-free DTaP vaccines. An association between neurodevelopmental disorders and thimerosal-containing DTaP vaccines was found, but additional studies should be conducted in order to confirm and extend this study.

Key Words: Autism, Neurodevelopmental disorders, Thimerosal, VAERS

Introduction

In recent years, thimerosal, an organic mercury compound that is metabolized to ethylmercury and thiosalicylate and has been present since the 1930s as a preservative in some vaccines and pharmaceutical products to prevent bacterial and fungal contamination, has come under scrutiny. It was determined by the US Food and Drug Administration (FDA) in 1999 under the recommended childhood immunization schedule, infants might be exposed to cumulative doses of ethylmercury that exceed some federal safety guidelines established for exposure to methylmercury, another form of organic mercury (1).

The hypothesis that exposure to thimerosal-containing vaccines could be associated with neurodevelopmental disorders is not established and rests on indirect and incomplete information, primarily from analogies with methylmercury and levels of maximum mercury exposure from vaccines given in children. The hypothesis is biologically possible, but the possible relationship between thimerosal from vaccines and neurodevelopmental disorders of autism, attention deficit/hyperactivity disorder (ADHD), and speech or language delay remains seriously suspect. As of the present, there are no peer–reviewed epidemiological studies in the scientific literature examining the potential association between thimerosal-containing vaccines and neurodevelopmental disorders. Here we show the first epidemiologic evidence, based upon tens of millions of doses of vaccine administered in the US that potentially associates increasing thimerosal from vaccines with neurodevelopmental disorders.

Methods

In this study, the incidence of neurodevelopmental disorders in a comparative examination between thimerosal-containing Diphtheria, Tetanus and acellular Pertussis (DTaP) and thimerosal-free DTaP vaccines based upon analysis of the Vaccine Adverse Events Reporting System (VAERS) database was undertaken using Microsoft Access. The VAERS database is an epidemiologic database maintained by the Centers for Disease Control and Prevention (CDC) since 1990. All adverse reactions are to be reported to the VAERS database as required by US law. The CDC requires written and telephonic confirmation of serious adverse reactions and follows up these patients one year latter. The FDA inquires into deaths reported to the VAERS database by contacting the patient's healthcare provider and physician. The FDA also continually monitors reports to the VAERS database to determine whether any vaccine or vaccine lot has a higher than expected incidence rate of events. The VAERS Working Group of the CDC, the FDA and us analyze and publish epidemiologic studies based upon analysis of the VAERS database (2-7).

The neurodevelopmental disorders we analyzed in this study were autism, mental retardation and speech disorders. These categories of adverse reactions were based upon descriptions of adverse reactions by those reporting them and by defined fields contained in the VAERS database. We determined the number of male and female reaction reports, the mean and standard deviation of age in years and mean and standard deviation of onset in days in those experiencing neurodevelopmental disorders following thimerosal-containing and thimerosal-free DTaP vaccines.

We hypothesize that DTaP vaccines, whether containing thimerosal or not, should have a similar incidence rate of adverse reactions. We analyzed DTaP administered by manufacturer, so that we could compare thimerosal-containing DTaP vaccines administered from 1992 through 2000 against thimerosal-free DTaP vaccines administered from 1997 through 2000. We used denominators obtained from the Biological Surveillance Summaries of the CDC to determine the number of doses of each manufacturer administered and based upon this information we were able to calculate incidence rates of adverse reactions following vaccination. We are precluded from giving incidence rates, the number of doses administered, or types of DTaP vaccine, because this information could reveal the identities of the manufacturers and the CDC claims this information is proprietary between them and the manufacturers (7).

We compared the incidence of adverse reactions following thimerosal-containing DTaP vaccines against thimerosal-free DTaP vaccines in order to determine relative risk, attributable risk, percent association and statistical significance. The relative risk value was obtained by dividing the incidence rate of the adverse reaction following thimerosal-containing DTaP vaccines by the incidence rate of the adverse reaction following thimerosal-free DTaP vaccines ([adverse reaction incidence following thimerosal-containing DTaP vaccines]/[incidence rate following thimerosal-free DTaP vaccines] = relative risk). The attributable risk value was determined by subtracting one from the relative risk value (relative risk – 1 = attributable risk). Percent association was calculated by dividing the relative risk value by the relative risk value plus one and multiplying this computed value by 100 ([relative risk/[relative risk + 1]] x 100). Statistical significance was determined by using Fisher's Exact Test. Our null hypothesis was that there would be a statistically similar incidence rate of adverse reactions following thimerosal-containing and thimerosal-free DTaP vaccines. We assumed that the incidence of adverse reactions following thimerosal-free DTaP vaccines was the expected rate and the incidence of adverse reactions following thimerosal-containing DTaP vaccines was the observed rate. The statistical package contained in Correl's Quattro Pro was used and a p value of 0.05 was considered significant.

In addition, in order to determine if there were potential biases in our data, we employed several controls. We examined the overall mean and standard deviation of the ages of thimerosal-containing and thimerosal-free DTaP vaccine adverse reactions reported to the VAERS, in order to ensure that both types of vaccines were administered to similar aged populations, because different aged populations may have a difference in the incidence of neurodevelopmental disorders. The mean ages of those reporting neurodevelopmental disorders following vaccination, may also help to determine whether successive doses of thimerosal-containing DTaP vaccines, buildup concentrations of thimerosal to toxic levels, resulting in neurodevelopmental disorders in vaccine recipients. The usual course of DTaP vaccine in children consists of primary immunizations administered at 2, 4 and 6 months, followed up by booster doses at 18 months and at 5 years. We also examined the incidence rate of acute adverse reactions reported to the VAERS database following thimerosal-containing and thimerosal-free DTaP vaccines including: deaths, seizures, vasculitis, Emergency Department (ED) visits, total reaction reports and gastroenteritis. This control served several purposes. First, if differences in manufacturing processes, other than the presence of thimerosal were present, there is a reasonable probability that this might have a significant impact on the incidence rate of acute adverse reactions. Second, if biased increased reporting rates of adverse reactions were present for thimerosal-containing DTaP vaccines, this would be reflected in an increased incidence rate of acute adverse reactions following thimerosal-containing DTaP vaccines in comparison to thimerosal-free DTaP vaccines. The years examined in this study also help to preclude the possibility of reporting biases based upon popular media publicity of an association between thimerosal and neurdevelopmental disorders in recent years because thimerosal-containing DTaP vaccines were analyzed for much earlier years (1992-2000), than thimerosal-free DTaP vaccines (1997-2000).

Results

We determined based upon our examination of the VAERS database that there were a total of 6,575 adverse reaction reports following thimerosal-containing DTaP vaccines and 1,516 adverse reaction reports following thimerosal-free DTaP vaccines reported to the VAERS database. We found that thimerosal-containing DTaP vaccines and thimerosal-free DTaP vaccines were administered to similar aged populations. The mean and standard deviations of the ages were 2.4 ± 3.2 years-old and 2.1 ± 2.8 years-old, respectively. In Table 1, we summarize the number of male and female reports, mean and standard deviation of age in years, and mean and standard deviation of onset in days of neurodevelopmental disorders observed following thimerosal-containing DTaP vaccines and thimerosal-free DTaP vaccines. Our data showed large male/female ratios in those children reported to have developed autism (17) and speech disorders (2.3) following vaccination with thimerosal-containing DTaP vaccines. However, the male/female ratio was significantly less appreciable in children reported to have developed mental retardation (1.2) following thimerosal-containing DTaP vaccines. The mean ages of children developing neurodevelopmental disorders following thimerosal-containing DTaP vaccines indicated that older children were primarily affected. In Table 2, we summarize the relative risk, attributable risk, percent association and statistical significance of neurodevelopmental disorders following thimerosal-containing DTaP vaccines in comparison to thimerosal-free DTaP vaccines. We found statistical increases in the incidence of autism, mental retardation and speech disorders following thimerosal-containing DTaP vaccines in comparison to thimerosal-free DTaP vaccines. The relative risks were greater than two for each type of neurodevelopmental disorder analyzed. In Table 3, we summarize the relative risk, attributable risk and percent association of the acute control adverse reactions we analyzed following thimerosal-containing DTaP vaccines in comparison to thimerosal-free DTaP vaccines. We found a slight increase in the incidence of seizures, ED visits and total reaction reports following thimerosal-containing DTaP vaccines in comparison to thimerosal-free DTaP vaccines. We also found that gastroenteritis, vasculitis and deaths occurred at comparable incidence rates following thimerosal-containing DTaP vaccines in comparison to thimerosal-free DTaP vaccines.

Discussion

The results of our analysis were extremely surprising. We observed statistically significant increases in the incidence rate of neurodevelopmental disorders following thimerosal-containing DTaP vaccines in comparison to thimerosal-free DTaP vaccines. We observed that the overall mean age for adverse reactions reported following thimerosal-containing DTaP vaccines and thimerosal-free DTaP vaccines were similar. We found that there were similar incidence rates of acute adverse reactions following thimerosal-containing DTaP vaccines, in comparison to thimerosal-free DTaP vaccines, indicating that potential differences in the manufacturing of DTaP vaccines analyzed outside of thimerosal concentrations or potential population reporting biases, may have had a limited effect on the general reactivity profiles of the DTaP vaccines examined. We also observed, based upon the mean ages of those developing neurodevelopmental disorders following thimerosal-containing DTaP vaccines that these reactions tended to occur in older children. This potentially may be explained by the toxic buildup of mercury from successive doses of thimerosal-containing DTaP vaccines.

A study performed by Magos et al. in rats compared the effects of the administration of similar doses of ethylmercury and methylmercury (8). They found that higher concentrations of inorganic mercury in the kidneys and brain were present in ethylmercury-treated rats compared to methylmercury-treated rats. They determined that there was little difference in the neurotoxicites of ethylmercury and methylmercury treated rats when effects on the dorsal root ganglia or coordination disorders were compared. The authors also determined that microgram quantities of organic-mercury alone in the rat brain were in some cases associated with neurotoxicity indicating that the presence of inorganic mercury was not necessary for neurotoxicity.

The long mean onset times observed in this study for neurodevelopmental disorders following thimerosal-containing DTaP vaccines from about 8 to 22 days may be indicative of the decomposition rates of thimerosal. It has been shown by Tan and Parkin that thimerosal *in vitro* decomposes in the presence of sodium chloride at approximately 4.3% per day (9). This means that during the 8 to 22 day temporal period of onset observed in this study for neurodevelopmental disorders approximately 34.4% to 94.6% of the thimerosal had decomposed into its derivatives. The authors also report that it would be expected that the ethylmercury would display similar complexion and chemical characteristics to methylmercury. Therefore, considering that sodium chloride is integrally involved in the functioning of the nervous system and kidneys, is not potentially surprising that mercury accumulates in these organs, and in the brain this accumulation manifests itself in the form of neurodevelopmental disorders in some children.

Bernard et al., have compared the similar biological abnormalities commonly found in autism and the corresponding pathologies arising from mercury exposure (10). Distinct similarities were found between autism and mercury exposure in their effects upon biochemistry, the immune system, the central nervous system structure, neurochemistry and neurophysiology. The authors report that mercury toxicity shows great variability in its effects on the individual, so that at the same exposure level, some will be affected severely while others will be asymptomatic. They provide the example of acrodynia, which arose in the early 20th Century resulting from the use of mercury teething powders which afflicted only 1 in 500-1,000 children given the same low dose. The authors conclude that due to the extensive parallels observed between autism and mercury exposure from thimerosal present in currently used vaccines the likelihood of a causal relationship is great.

We were initially highly skeptical that differences in the concentrations of thimerosal in vaccines would have any effect on the incidence rate of neurodeveopmental disorders following childhood immunization. The results of our analysis however suggest that children who received an additional 75-100 µg of thimerosal from thimerosal-containing DTaP vaccines may have an associated increase in neurodevelopmental disorders based upon analysis of the VAERS database. Despite showing similarities in the ages of vaccine recipients between thimerosal-containing and thimerosal-free DTaP vaccines, similarities in the incidence rate of acute control reactions following thimerosal-containing and thimerosal-free DTaP vaccines and a increased age of onset of neurdevelopmental disorders in those receiving thimerosal-containing DTaP vaccines, there may be factors other then thimerosal concentrations that potentially lead to differences in the incidence rates of neurodevelopmental disorders observed in this study.

The relative infrequency of neurodevelopmental disorders observed following thimerosal-containing vaccines may in part reflect the fact that the association between thimerosal and neurodevelopmental disorders was not known among those physicians and therefore was underreported to the VAERS database and, in addition, may indicate that other factors than just thimerosal may effect the incidence rate of neurodevelopmental disorders. These factors may include the possibility that mercury is cleared at different rates, susceptibility among children may change with age or developmental status and there may be variation in genetic composition among different children. It is possible that these factors may work independently, or more probably, they work synergistically to produce a neurodevelopmental response in a susceptible child.

It has also been hypothesized by Wakefield et al. that there may be a specific viral pathogenic mechanism for a new variant of inflammatory bowel disease among children with developmental disorders (11, 12). They have recently shown a statistical increase in the detection of measles viral genes in gastrointestinal tissues in children with neurodevelopmental conditions in comparison to a control population (12). Krause et al. have reported that various immune system abnormalities, including autoimmunity and defects in different subsets of immune cells, have been reported in children with autistic disorders, suggesting that immune factors may also play a role in the development of autism (13).

Conclusion

In light of the fact that many additional factors may play a potential role in the development of neurodevelopmental disorders in children, the observed statistical increase in neurodevelopmental disorders in children receiving thimerosal-containing DTaP vaccines may reflect a synergistic effect of multiple factors in a susceptible child. We recommend additional studies be conducted in order to confirm and extend the results of this study. We suggest, that even though there may be other factors related to the incidence of neurodevelopmental disorders in children, manufacturers should consider removing thimerosal from vaccines either by using another preservative or by producing single dose vials so that no preservative is necessary, for it is better to be safe than sorry. Despite these negative findings concerning the preservative thimerosal, vaccination has been and will continue to be an invaluable asset to control potentially debilitating and deadly infectious diseases.

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Table 1. A summary of neurodevelopmental disorders reported following thimerosal-containing DTaP vaccines and thimerosal-free DTaP vaccines

Type of Reaction (Vaccine Type)	Number of Female Reports	Number of Male Reports	Mean Age (Years)	Mean Onset (Days)
Autism (Thimerosal)	1	17	1.7 ± 1.1	22 ± 43
Mental Retardation (Thimerosal)	17	20	1.4 ± 2.0	10 ± 15
Speech Disorders (Thimerosal)	8	18	2.9 ± 1.9	7.7 ± 15.4
Autism (Thimerosal-free)	0	1	1.2	-
Mental Retardation (Thimerosal-free)	0	2	1.6 ± 0.4	15
Speech Disorders (Thimerosal-free)	1	3	3.4 ± 2.2	3.4 ± 5.9

There were a total of 6,575 adverse reaction reports following thimerosal-containing DTaP vaccines and 1,516 adverse reaction reports following thimerosal-free DTaP vaccines reported to the VAERS database.

Table 2. A summary of the incidence of neurodevelopmental disorders following thimerosal-containing DTaP vaccines in comparison to thimerosal-free DTaP vaccines

Type of Reaction	Relative Risk	Attributable Risk	Percent Association	Statistical Significance
Autism	6.0	5.0	86	$p < 0.05$
Mental Retardation	6.1	5.1	86	$p < 0.002$
Speech Disorders	2.2	1.2	69	$p < 0.05$

Table 3. A summary of the incidence of acute control adverse reactions following thimerosal-containing DTaP vaccines in comparison to thimerosal-free DTaP vaccines

Type of Reaction	Relative Risk	Attributable Risk	Percent Association
Deaths	1.0	0.0	50
Vasculitis	1.2	0.2	54
Seizures	1.6	0.6	61
Emergency Department Visit	1.4	0.4	58
Total Reaction Reports	1.4	0.4	58
Gastroenteritis	1.1	0.1	52

Exposure Limits for Mercury & Childhood Prospective Assessment

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** For an average weight newborn (3.3 Kg), receiving a Hep B vaccine = 12.5ug

First Day Excess Max Dose of Mercury

EPA = 0.1ug/Kg body weight/day = 38 x Max Dose

ATSDR = 0.3ug/Kg body weight/day = 13 x Max Dose

FDA = 0.4ug/Kg body weight/day = 10 x Max Dose

10 Days Excess Max Dose of Mercury

EPA = 0.1ug/Kg body weight/day = 3.8 x Max Dose

ATSDR = 0.3ug/Kg body weight/day = 1.3 x Max Dose

FDA = 0.4ug/Kg body weight/day = 1.0 x Max Dose

** For an average weight 2 month-old (4.6 Kg), receiving a DTP, Hib, Hep B = 62.5ug

First Day Excess Max Dose of Mercury

EPA = 0.1ug/Kg body weight/day = 128 x Max Dose

ATSDR = 0.3ug/Kg body weight/day = 42 x Max Dose

FDA = 0.4ug/Kg body weight/day = 32 x Max Dose

10 Days Excess Max Dose of Mercury

EPA = 0.1ug/Kg body weight/day = 12.8 x Max Dose

ATSDR = 0.3ug/Kg body weight/day = 4.2 x Max Dose

FDA = 0.4ug/Kg body weight/day = 3.2 x Max Dose

** For an average weight 4 month-old (6.5 Kg), receiving a DTP, Hib, Hep B = 62.5ug

First Day Excess Max Dose of Mercury

EPA = 0.1ug/Kg body weight/day = 96 x Max Dose

ATSDR = 0.3ug/Kg body weight/day = 32 x Max Dose

FDA = 0.4ug/Kg body weight/day = 24 x Max Dose

10 Days Excess Max Dose of Mercury

EPA = 0.1ug/Kg body weight/day = 9.6 x Max Dose

ATSDR = 0.3ug/Kg body weight/day = 3.2 x Max Dose

FDA = 0.4ug/Kg body weight/day = 2.4 x Max Dose

** For an average weight 6 month-old (7.21 Kg), receiving a DTP, Hib = 50ug

First Day Excess Max Dose of Mercury

EPA = 0.1ug/Kg body weight/day = 69 x Max Dose

ATSDR = 0.3ug/Kg body weight/day = 23 x Max Dose

FDA = 0.4ug/Kg body weight/day = 17 x Max Dose

10 Days Excess Max Dose of Mercury

EPA = 0.1ug/Kg body weight/day = 6.9 x Max Dose

ATSDR = 0.3ug/Kg body weight/day = 2.3 x Max Dose

FDA = 0.4ug/Kg body weight/day = 1.7 x Max Dose

Vaccine Safety Datalink (VSD) Data Concerning Mercury From Vaccines and Neurodevelopmental Disorders in Children

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We analyzed the Vaccine Safety Datalink (VSD) 2/29/00 Report, Phase I by the CDC. Specifically, we analyzed the distribution of the relative risks for neurodevelopmental delay adverse events including: neurodevelopmental neurologic disorders, autism, attention deficit disorder and developmental speech delay reported following exposure to 50ug, 62.5ug and 75ug of mercury from thimerosal contained in vaccines administered within the first three months of a child's life. Our statistical null hypothesis was that the concentration of mercury from thimerosal contained in vaccines administered within the first three months of a child's life should have no effect on the incidence rate of neurodevelopmental delay adverse events reported to the VSD. In analyzing the distribution we applied exponential trend -lines of best fit to describe the distribution of the relative risks of each of the adverse neurodevelopmental delay adverse events analyzed. We found that it was statistically unlikely ($p < 0.05$) that by mere chance (i.e. a probability of less 5%) of observing a distribution of increasing relative risks for each type of neurodevelopmental delay adverse event examined with an increasing exposure to mercury from thimerosal contained in vaccines administered. For each type of neurodevelopmental delay adverse event examined, the results were as follows:

Figure 1. This figure shows that there is an over 99% probability that the exponentially distributed increasing relative risks for developmental neurologic disorders following increasing mercury concentrations from vaccines thimerosal contained in vaccines administered within the first three months of a child's life was not due to chance.

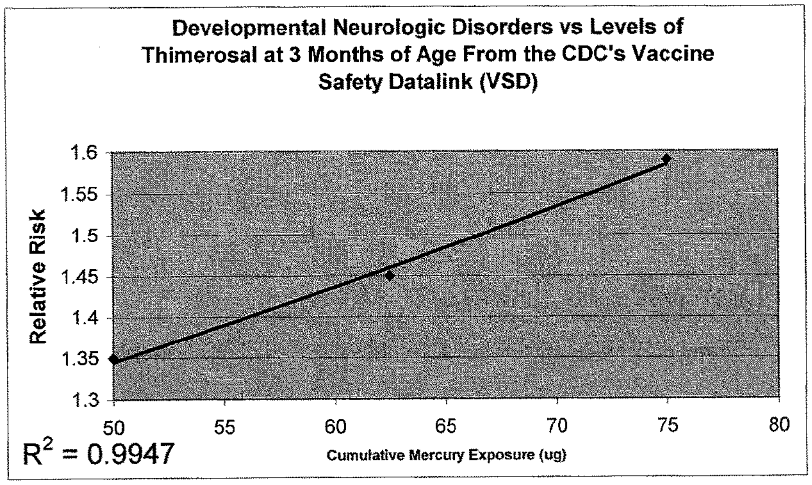


Figure 2. This figure shows that there is an over 95% probability that the exponentially distributed increasing relative risks for autism following increasing mercury concentrations from vaccines thimerosal contained in vaccines administered within the first three months of a child's life was not due to chance.

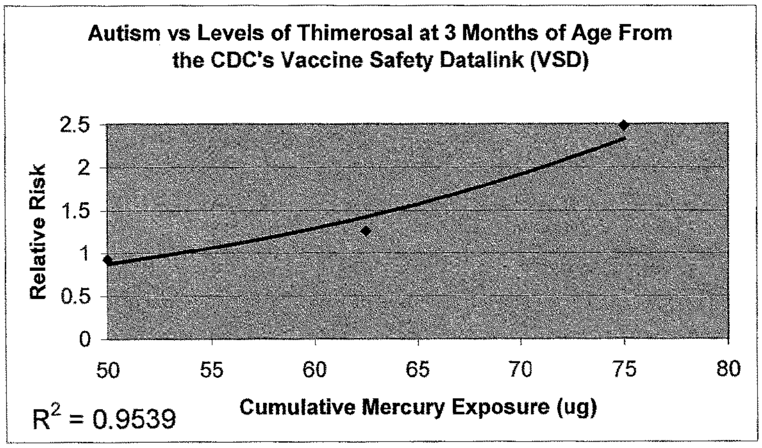


Figure 3. This figure shows that there is an over 95% probability that the exponentially distributed increasing relative risks for attention deficit disorder following increasing mercury concentrations from vaccines thimerosal contained in vaccines administered within the first three months of a child's life was not due to chance.

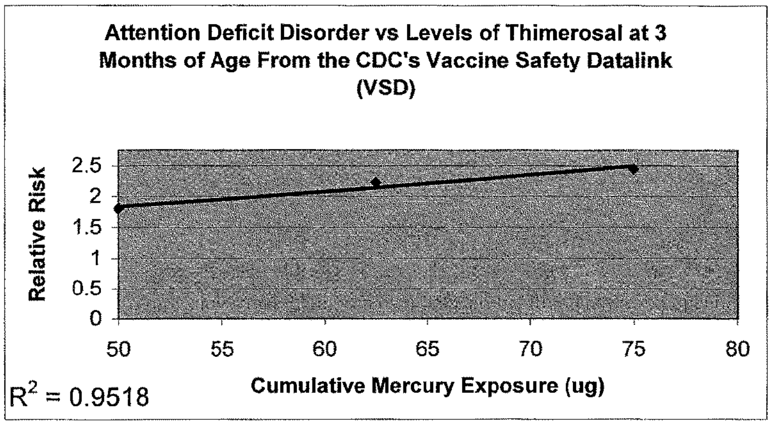
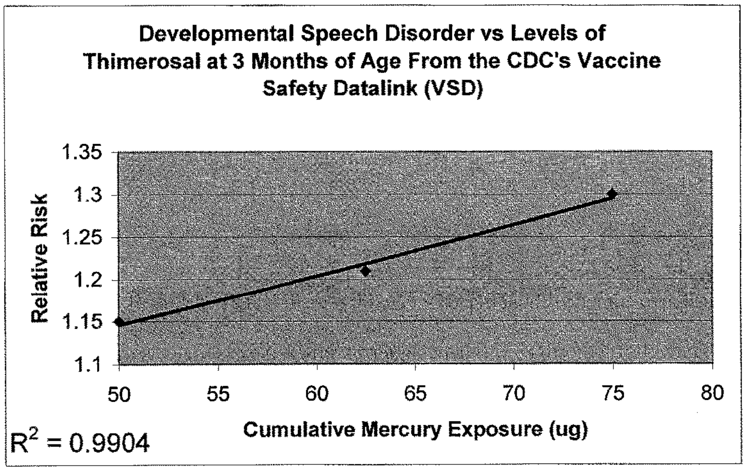


Figure 4. This figure shows that there is an over 99% probability that the exponentially distributed increasing relative risks for developmental speech disorder following increasing mercury concentrations from vaccines thimerosal contained in vaccines administered within the first three months of a child's life was not due to chance.



These observations for neurodevelopmental disorders were in sharp to contrast to the relative risk of other adverse events reported to the VSD following increasing exposure to thimerosal contained in vaccines administered within the first three months of a child's life. These other types of adverse events such as renal disorders, epilepsy, infantile cerebral palsy had no correlation in the distribution of the relative risks of these adverse events with increasing mercury exposure from the thimerosal contained in vaccines administered within the first three months of a child's life, and in general the relative risks for these adverse events remained close to one. The reproducibility of the increasing exponential relative risk of neurodevelopmental disorders reported following increasing mercury from thimerosal contained in the vaccines administered within the first three months of a child's life, in combination with the absence of a correlation between unrelated neurodevelopmental disorder adverse events with increasing mercury from thimerosal contained in vaccines, suggests that there may be an association between neurodevelopmental disorders an increasing mercury exposure from thimerosal contained in vaccines administered within the first three months of a child's life. It should be noted that these results should be interpreted with caution, since our analyses were of a preliminary report (VSD 2/29/00 Report, Phase I) by the CDC of the VSD database.

Pediatric MMR Vaccination Safety

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ABSTRACT

Measles, mumps and rubella are viral infections that have the potential to result in globally destructive disorders. Measles, mumps and rubella (MMR) vaccine has helped to dramatically reduce the number of cases of measles, mumps and rubella infection, as well as to reduce the amount of pain and suffering associated with each of these natural infections. The purpose of this study was to analyze the incidence of serious neurologic disorders in a comparative examination between MMR vaccine and a vaccine control group. The Vaccine Adverse Events Reporting System (VAERS) database was analyzed for the incidence rate of permanent brain damage, cerebellar ataxia, autism and mental retardation reported following MMR vaccine and diphtheria, tetanus and whole-cell pertussis (DTwcP) containing-vaccines from 1994 through 2000 among those residing in the US. There were statistically significant increases in the incidence of serious neurologic disorders following pediatric MMR vaccine in comparison to DTwcP vaccine. It is clear that with the potentially globally destructive effects of natural measles, mumps and rubella infections that continued vaccination is necessary, but improvements in MMR vaccine strategies should be sought to improve its safety.

KEY WORDS: autism, mental retardation, neurodevelopmental disorders, MMR, VAERS.

INTRODUCTION

Measles formerly afflicted virtually all children before they reached adolescence in the United States. It is a viral infection caused by a member of the paramyxovirus group. Conventionally, the diagnosis of measles is made clinically on the basis of its signs and symptoms, which include a characteristic rash. The diagnosis can be confirmed by a laboratory test that detects antibodies to the measles virus. The disease can be quite debilitating, and its complications are among the most serious consequences of childhood exanthematous infections. These include otitis media, croup, diarrhea, hemorrhagic rash, pneumonia, parainfectious encephalitis and subacute sclerosing panencephalitis.[1] The currently used Enders strain measles vaccine is a live more-attenuated vaccine derived from the Edmonston B strain by 40 passages through chicken embryo cells that were maintained at a lower than optimal temperature.[2]

Unlike measles, mumps is not considered a globally devastating disease. Nevertheless, because of its complications, it was targeted for prevention by use of a vaccine. The complications that prompted this were epididymoorchitis, aseptic meningitis, menigoencephalitis and deafness.[3] The currently used live mumps vaccine in the United States, was developed by passing the Jeryl Lynn strain of mumps through numerous passages in vitro, first in embryonated hen's eggs and then in chicken embryo cells.[4]

Rubella is commonly a mild disease; it afflicts children and young adults. It is characterized by erythematous, maculopapular, discrete rash; postauricular and suboccipital lymphadenopathy; and minimal fever. The disease is caused by an RNA virus belonging to the togavirus family. It can be transmitted transplacentally to a fetus, sometimes with devastating results. The incubation period of natural rubella is 14 to 21 days, with the characteristic rash appearing within 14 to 17 days after exposure. The patient is usually asymptomatic in the first week after exposure. By early in the second week, lymphadenopathy becomes apparent and rubella virus can usually be cultured from nasopharyngeal secretions. By the end of the second week, virus is detectable in the blood. After the 14 to 21 day incubation period, a one to five day prodromal illness consisting of malaise, low-grade fever, mild conjunctivitis and, occasionally, arthralgia can occur, but it may be minimal or absent. The rash, in most cases, appears at this time, beginning on the face and neck and spreading quickly to the trunk and extremities. It usually lasts about for about five days. The current live rubella vaccine, is a human diploid fibroblast vaccine, RA 27/3, that was licensed for use in the United States in 1979.[5]

These three different live viral vaccines are combined to produce the measles, mumps and rubella (MMR) vaccine analyzed in this study. The American Academy of Pediatrics recommends that MMR vaccine be given at age 15 months and at entry into middle or junior high school. The Advisory Committee on Immunization Practices recommends that MMR be administered at 15 months and then again at school entry at age four to six years. The strength of the US MMR vaccination program has helped to dramatically reduce the number of cases of measles, mumps and rubella infection, as well as to reduce the amount of pain and suffering associated with each of these natural infections. Despite the undoubtable positive effects of MMR vaccination, there have been a number of recent publications that implicate the potential for debilitating serious reactions following pediatric immunization with MMR vaccine.[6-8]

The purpose of this analysis was to analyze the incidence rate of serious neurologic symptoms following primary pediatric MMR immunization of children based upon analysis of the Vaccine Adverse Event Reporting System (VAERS) database. The VAERS database is an epidemiologic database that has been maintained by the Centers for Disease Control and Prevention (CDC) since 1990. All adverse reactions following vaccines are to be reported to this database as mandated by US law. The CDC requires written and telephonic confirmation of all serious adverse reactions and follows up serious reactions one-year latter to determine whether or not the patient had fully recovered. We and the VAERS Working Group of the CDC, analyze and publish epidemiologic studies based upon review of the VAERS database. The VAERS working group has published that VAERS is simple for reporters to use, flexible by design and that its data are available in a timely fashion.[9]

MATERIALS AND METHODS

In this study, the VAERS database was analyzed retrospectively for serious neurologic symptoms following primary pediatric MMR immunization from 1994 through 2000 that developed within 30 days among those residing in the US. The serious neurologic adverse reactions analyzed included: cerebellar ataxia, autism, mental retardation and permanent brain damage. Descriptions of adverse reactions relied upon those reporting them and were defined by the reporting fields contained in the VAERS database. The calculated incidence rates were obtained from the estimates of the Biological Surveillance Summaries received from the CDC, and by analyzing the number of children in each year's birth cohort from 1994 through 2000 and the CDC estimates of the percent coverage of each yearly birth cohorts with primary pediatric MMR vaccination.

The estimates indicate that 24,825,174 doses of primary MMR vaccine were administered from 1994 through 2000. Diphtheria, Tetanus and whole-cell pertussis (DTwcP) containing-vaccine serious neurologic reactions (a control) reported to VAERS from 1994 through 2000 that developed within 30 days among those residing in the US were analyzed. The CDC estimates indicate that 63,035,269 doses of DTwcP were administered from 1994 through 2000. The incidence rates of serious neurologic reactions following DTwcP vaccine recipients provided a background rate to compare against the incidence rates of serious neurologic reactions in primary pediatric MMR vaccine recipients.

A search for the incidence rate of a specific adverse reaction to one vaccine would be expected to be similar to the incidence rate following another vaccine administered to a similarly aged population; whatever the inherent limitations in the precision of reported adverse reactions to the VAERS database, the would be expected to equally affect the VAERS submissions of both vaccines under study. Similarly, the number of doses of a type of vaccine administered, based upon the CDC estimates, should be unbiased because the limitations in the CDC estimates, they should equally apply to each vaccine under study. The assumption of equal reactogenicity between vaccines, forms the basis of our null hypothesis.

The incidence rate of an adverse reaction following MMR vaccine in comparison to the incidence rate of an adverse reaction following the DTwcP vaccine control group determines the relative risk, attributable risk, the percent association and statistical significance of the adverse reaction for MMR vaccine. The relative risk value is obtained by dividing the incidence rate of the adverse reaction following MMR vaccine by the incidence rate of the adverse reaction following the DTwcP vaccine control group. The attributable risk value is determined by subtracting one from the relative risk. The percent association value is calculated by dividing the relative risk value by the relative risk value plus one and multiplying this computed value by 100. Statistical significance was determined by using a χ^2 2x2 contingency table, which assumed that the total number of adverse reactions following the DTwcP control vaccine and the number of doses administered for the time period examined where the expected values and the total number of adverse reactions following the primary pediatric MMR vaccine under study and the number of doses administered for the time period examined were the observed values. The statistical package contained in Corel's Quattro Pro was used and a p value of 0.05 was accepted as statistically significant.

RESULTS

In Table 1, we summarize serious neurologic symptoms reported to the VAERS database following primary pediatric MMR vaccination. We analyzed the number of male and female reaction reports, mean and standard deviation of age in years, mean and standard deviation of onset in days and incidence per million MMR vaccinations. We found the male/female ratios for autism (3.6) and mental retardation (2.0) indicated that these reactions more predominantly occurred in males, whereas cerebellar ataxia and permanent brain damage were fairly evenly divided between male and female vaccine recipients. The overall mean age was approximately 1.8 years-old and the mean onset time range from about 5 to 10 days following MMR immunization. We found that serious neurologic illnesses were reported following DTwcP vaccine as follows: 0.22 per million DTwcP vaccines for cerebellar ataxia, 0.29 per million DTwcP vaccines for autsim, 0.84 per million DTwcP vaccines for mental retardation and 0.30 per million DTwcP vaccines for permanent brain damage. In Table 2, we summarize the relative risk, attributable risk, percent association, statistical significance and 95% relative risk confidence intervals for serious neurologic adverse reactions reported following primary pediatric MMR vaccination in comparison to DTwcP vaccination. We found that cerebellar ataxia, autism, mental retardation and permanent brain damage were all statistically significantly increased following primary MMR vaccination in comparison to DTwcP vaccination.

DISCUSSION

The results of our analysis showed that primary pediatric MMR vaccination in children was associated with a marked increase in serious neurologic disorders in comparison to DTwcP vaccination. The increase was statistically significant for cerebellar ataxia, autism, mental retardation and permanent brain damage following primary pediatric MMR vaccination in comparison to DTwcP vaccination. This result is rather remarkable considering that DTwcP vaccination itself has been accepted in the scientific and medical communities to be responsible for permanent neurologic sequella in children.[10-13]

Similarly, previous studies have reported on serious untoward neurological disorders following measles, mumps and MMR vaccinations. These studies also observed similar temporal relationships between the onset of serious neurological disorders and vaccination as was observed in this study. Weibel *et al.*, have reported that the clustering of reactions on days eight and nine following measles-containing vaccines suggests that there is casual relationship between measles vaccine and encephalopathy.[8] In Denmark it has been reported there were 24 reports of temporary gait disturbances after MMR vaccine.[14] The median onset following MMR vaccination was 6 days (range 3-25 days). Patients usually recovery occurred by a mean of 8 days (range 1-100 days), but 1 child still had gait disturbances 3 months after vaccination. They further observed that 8 of the 24 children had a possible cerebral disorder and 3 children seen by a pediatric neurologist were diagnosed with a cerebellar disorder and ensuing ataxia. Cerebellar ataxia has been reported after natural measles, mumps and rubella. The established rate of gait disturbances following MMR vaccine was 6 per 100,000 vaccinees. The authors reported that the symptoms usually disappeared within a few days but in some children they can last several months with cerebral involvement indicating a more severe disorder. Another study, analyzed 23 cases of neurological disorders that were reported to the CDC from January 1965 to February 1967 following 1.4 million doses of live measles vaccine.[15] The mean time of onset was 8.7 days for reactions following live measles vaccine. The incidence rate of encephalitis following live measles vaccine was 1 per 643,500 immunizations and of chronic damage was 1 per 5 million immunizations. A study conducted from 1976 to 1989 in the Federal Republic of Germany analyzed the adverse effects of approximately 5.5 million doses of vaccines containing measles, some given as monovalent vaccines, some as trivalent and some as bivalent vaccines were administered.[16] During this time, there were 433 spontaneous case reports of side-effects (1/12,700 doses). The most common reactions were as follows: 264 reports of fever, 159 reports of rash, 75 upper respiratory infection reports and 21 reports of conjunctivitis. These reactions occurred 7-14 days following vaccination, with 2-7 days being the next most common temporal period. There were 57 reports of parotitis between 7 days and 30 days (1 per 90,000 vaccinations), 6 reports of orchitis (1 per 1.25 million vaccinations), 11 reports of thrombocytopenia (1 per 600,000 vaccinations), 41 reports of measles seizures, all after measles-containing immunizations, 7 of these were without fever, (1 per 180,000 vaccinations), 13 reports of gait disturbances (1 per 420,000 vaccinations), 16 reports of encephalitis/meningitis (1 per 1 million vaccinations) and transient EEG changes observed in 3% of vaccinees. In a study conducted in the United States from 1963 through 1971, 84 cases of neurological disorders with onset of less than 30 days were reported after live measles virus vaccination.[17] Among these 84 cases, 76% had an onset from 6 to 15 days following immunization. The authors conclude that the clustering suggests that some may have been caused by the vaccine. The incidence rate of neurological disorders based upon this study was 1 per 1.16 million live measles vaccinations. Another study found 18 cases of neurological complications following live measles vaccine administered between 1971 to 1978 in Hamburg, Germany.[18] A causal connection was assumed by the author in 14 of the cases, resulting in an incidence of 1 per 2,500 vaccinees. The author observed an incidence of 1 per17,650 vaccinees of abortive encephalopathy following live measles vaccination.

The pathogenesis of serious neurological reactions observed following MMR vaccination in this study and in other previous studies most likely reflects the direct effects of the three live viruses present in MMR vaccine. It has been observed that patients following MMR vaccination develop many of the same symptoms as if they were infected with natural measles or mumps infections. Patients following vaccination with MMR have reported development of rashes, fevers, gastrointestinal symptoms, gait-disturbances and neurological disorders. The overall result of the similarities between natural infection and MMR vaccination, means that effects of these natural viral infections must be taken seriously as possible occurring at a low frequency following vaccination.

It has been observed that natural exposure to live viruses can result in autism.[19,20] Another study describes some of the endoscopic and pathological characteristics of children with developmental disorders.[21] An endoscopically and histologically consistent pattern of ileocolonic pathology has been identified in a cohort of children with developmental disorders. Illeal lymphoid nodular hyperplasia was found in 54 out of 58 (93%) affected children and 5 out of 35 (14.3%) in controls ($p < 0.001$). Histologically reactive follicular hyperplasia was present in 46 out of 52 (88.5%) in affected patients and 4 out of 19 (29%) in ulcerative colitis controls ($p<0.01$). Measles virus has been associated with immunodysreglation and autism. It follows that those children vaccinated with live MMR vaccine may on rare occasions develop similar conditions.

It has recently been hypothesized that by combining the three live viral components of MMR vaccine that there is an increased severity of adverse reactions following MMR vaccination then would be expected based upon the reactogenicity profiles of each of the component vaccines of MMR vaccine administered individually.[7] We have analyzed other studies that have examined the reactivity of individual components of MMR and combined MMR vaccines, and found this to be true. A Japanese study has analyzed the incidence rate of meningitis following mumps vaccine and MMR vaccine.[22] They found that in laboratory-confirmed mumps vaccine-related meningitis that patients developed at an increased relative risk following MMR vaccine in comparison to mumps vaccine as follows: fever (relative risk = 4.1), vomiting (relative risk = 4.8), headache (relative risk = 2.0), meningeal irritation signs (relative risk = 4.8), convulsions (relative risk = 7.5) and parotid swelling (relative risk = 2.0). They also reported that there was a statistically significant difference in the time interval from vaccination to the onset of meningitis following MMR vaccine in comparison mumps vaccine. Our review of a British study, found that there was an increased relative risk in the incidence rate of fever (relative risk = 1.1), rash (relative risk = 1.6) and off-food (relative risk = 1.4) adverse reactions following MMR vaccine in comparison to measles vaccine.[23]

In order to alleviate many of the difficulties encountered with the MMR vaccine, we suggest that a killed MMR vaccine should be made available because it might help to reduce the number and severity of many of the adverse reactions adverse reactions observed following live MMR vaccine. A study conducted in England, by the British Medical Research Council, compared the safety and efficacy of a killed measles vaccine followed by a live measles vaccine against that of a live measles vaccine.[24] The study involved about 10,000 children vaccinated with a killed measles vaccine followed by a live measles vaccine, 10,000 children vaccinated with live measles vaccine and 16,000 children that did not receive any vaccine. The efficacy portion of the study showed that those vaccinated with the combination of a killed measles vaccine followed by a live measles vaccine developed measles at a rate of only 12 per 1,000 children six months following vaccination, whereas those vaccinated with the live measles vaccine developed measles at a rate of 16 per 1,000 children and those that went unvaccinated developed measles at a rate of 94 per 1,000 children. The safety portion of the study showed that seizures reported following 21 days vaccination occurred randomly following killed measles vaccine followed by live measles vaccine at an incidence rate of 0.7 per 1,000 children, whereas they occurred non-randomly (peak from 6-9 days) following live measles vaccine at an incidence rate of 1.9 per 1,000 children. The incidence of seizures in the unvaccinated group was 0.3 per 1,000 children. Additionally, there were marked decreases in the incidence of vomiting, malaise, rash and fever following killed measles vaccine followed by live measles vaccine in comparison live measles vaccine. The killed measles vaccine used in this study was manufactured by Pfizer Ltd. We also suggest that if the current live MMR vaccine is to remain in use that parents should at least have the option to administer each of the components of MMR vaccine individually at different times.

In conclusion, this study showed the rather remarkable statistically significant increase in serious neurologic conditions following primary pediatric MMR vaccination in comparison to a DTwcP vaccine control group. This finding confirms and extends a number of previous publications that patients are increased risk for developing serious neurologic disorders for about 5-10 days following pediatric MMR vaccination. The pathogenesis of these reactions appears to follow a similar course as the natural viral infections. In order to elevate the potential for serious neurologic disorders following primary pediatric MMR vaccination, we suggest that killed MMR vaccine be made available and if the live MMR vaccine is continued to be used that parents should at least have the option to take each viral component of MMR vaccine administered separately. Those children who develop sequella following MMR vaccine should report their reactions to the VAERS database and should also apply for compensation under the no-fault Vaccine Compensation Act. The VAERS program can by reached 24 hours a day at 1-800-822-7967 and the Vaccine Compensation Act can be reached at 1-800-338-2382. It is clear that with the potentially globally destructive effects of natural measles, mumps and rubella infections that continued vaccination is necessary, but improvements in MMR vaccine strategies should be sought to improve its safety.

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Tables

Table 1. A summary of serious neurologic reactions following MMR vaccination

Type of Reaction	Number of Male Reaction Reports	Number of Female Reaction Reports	Mean Age (Years)	Mean Onset (Days)	Incidence per Million MMR Vaccines
Cerebellar Ataxia	23	21	1.4 ± 0.66	4.9 ± 4.7	1.8
Autism	29	8	1.8 ± 1.1	6.5 ± 7.2	1.5
Mental Retardation	23	12	1.9 ± 2.0	5.5 ± 6.0	1.4
Permanent Brain Damage	8	9	1.9 ± 1.2	9.7 ± 8.4	0.69

Table 2. A comparison of serious neurologic reactions following MMR vaccination in comparison to DTwcP vaccination

Type of Reaction	Relative Risk	Attributable Risk	Percent Association	Statistical Significance	95% Relative Risk Confidence Interval
Cerebellar Ataxia	8.2	7.2	89	$p < 0.0001$	4.4 to 15
Autism	5.2	4.2	84	$p < 0.0001$	3.0 to 9.2
Mental Retardation	1.7	0.7	63	$p < 0.05$	1.1 to 2.6
Permanent Brain Damage	2.3	1.3	70	$p < 0.05$	1.2 to 4.4

PROBLEMS WITH OBTAINING ACCESS TO THE VSD DATABASE

The following is a timeline of events that have occurred with regards to our obtaining access to the Vaccine Safety Datalink (VSD):

1) August 1- 11, 2002: We made several phone calls to Dr. Robert Chen's office at the Centers for Disease Control and Prevention (CDC), but were unable to reach him, so we left him several messages stating who we were and we were interested in obtaining access to the VSD (Exhibit 1).
2) August 12, 2002: We sent an email to Dr. Robert Chen asking for formal access to the VSD and asking what necessary arrangements did we have to make (Exhibit 1).
3) August 13, 2002: We received a telephone call from Dr. Chen's office instructing us to put into writing our formal request for access to the VSD and to send our request to Julie Gee, the VSD Project Coordinator. We were told that we would then be able to access the VSD.
4) August 14, 2002: We sent our formal written request to Julie Gee requesting formal access to the VSD and asked what were the necessary arrangements by next-day delivery mail (Exhibit 2).
5) August 30, 2002: We received a letter from Dr. Chen stating that he received our written request regarding access to the VSD and instructed us to go to the CDC's website for further details on the next steps needed (e.g., proposal preparation) (Exhibit 3).

6) September 5, 2002: We sent a 3 page proposal as per the instructions on the CDC's website to obtain formal access to the VSD database by next-day delivery mail (Exhibit 4).
7) September 24, 2002: We received a letter from William Broom stating that he received our proposal to analyze the VSD data. He stated that our proposal needed to be modified and resubmitted (Exhibit 5).
8) September 26, 2002: We submitted our 37 page modified proposal by next-day delivery mail (Exhibit 6).
9) October 24, 2002: We received a letter from William Broom stating that he received our proposal to analyze the VSD. He stated that our proposal needed to be modified further and resubmitted (Exhibit 7).
10) October 29, 2002: We submitted our 153 page further modified proposal by next-day delivery mail (Exhibit 8).
11) November 25, 2002: We received a letter from William Broom stating that he received our proposal to analyze the VSD. He stated that our proposal needed to be modified further and resubmitted (Exhibit 9).

Our current situation is one in which we have communicated with the CDC for more than 4 months and we have yet to receive an initial approval by the CDC for our proposal to analyze the VSD. The CDC claims that once they approve our proposal to analyze the VSD, we will then be provided with a point of contact at the relevant Managed Care Organization (MCO)s' Institution Review Boards (IRB)s (Exhibit 10). At this point, we will then have to meet the necessary requirements instituted by each MCOs' IRBs without any involvement from the CDC (Exhibit 10) It is unclear how long each MCOs'

IRBS will take to review our proposal or even in what manner the review process will take at each of the MCOs IRBs. Once we have obtained approval documentation from the different IRBs we must provide this documentation to the CDC (Exhibit 10). The CDC says that we will then have to pay the appropriate user fees (Exhibit 10). Once the user fees have been paid, the CDC will then prepare the study specific dataset so that it can be analyzed with SAS statistical software (Exhibit 10).

The CDC states that the external researcher will then need to make arrangements with CDC/NIP for a time when the RDC in Hyattsville, MD is available and CDC/NIP can provide a staff person to help with technical questions and monitor the progress of the external researcher (Exhibit 10). The CDC states, again that user fees must be paid and abide by the standard practices of the RDC, which include a restriction on equipment that can be brought in to the RDC, signing agreements to maintain confidentiality, and reviewing all results for any potential breaches in confidentiality (Exhibit 10). In addition, proposals will be processed at the CDC and datasets will be retrieved or created on a first come-first severed basis. Depending on the number of requests for data from the VSD data files that are received, response time may vary (Exhibit 10).

The CDC states that the RDC is a research facility located in the CDC's National Center for Health Statistics facility in Hyattsville, MD (Exhibit 11). Persons wishing to use the Center must sign an agreement to maintain the confidentiality of the data they will analyze (Exhibit 11). External researchers are not allowed to bring in cell phones, pagers, or other devices that would allow them to communicate while in the RDC with persons on the outside (Exhibit 11). All output is subject to disclosure review before it can be removed from the RDC (Exhibit 11). Disclosure review will include reviewing all computer output for geographic or patient-level data (Exhibit 11). Output will be restricted to summary tables of geographic or patient-level data (e.g. line listings of diagnosis by study-id will be prohibited) (Exhibit 11). External researchers must pay user fees in advance; which will cover the preparation of study specific datasets, monitored analysis of VSD data within the RDC, and use of the research facility (Exhibit 11). Researchers may only work at the RDC under the supervision of approved staff during normal working hours (8:00am to 5:00pm) (Exhibit 11). Usage of NCHS RDC is on a first come, first served basis due to limited space and resources (Exhibit 11). In addition, no more than 3 external researchers from a given proposal may work at the RDC at any one time (Exhibit 12).

Conclusion

In conclusion, after more than 4 months of work we are nowhere near getting access to the VSD. It is not clear if we will ever get the access we have requested. Most of our paper work should not have been necessary. Basically, we requested initially, that we be allowed to repeat studies on the VSD that we have already done on the VAERS database. These studies have been peer-reviewed and in fact published in the medical literature. Therefore, they have already been shown to be appropriate and scientifically valid.

We cannot even find out what it will cost even if we do get the permission. If we do get the permission we will be treated in a manner not appropriate for research scientists. Our access will be extremely limited. If our investigations do lead to interesting new ideas for further studies as they almost invariably do, we will have to go through the process all over again.

We think that we and others should be given free access to the VSD on a similar basis as we were given access to VEARS as was promised in the CDC Press release of 8/30/2002 (Exhibit 13). The issues of confidentiality have already been addressed in VAERS and can be handled in a similar way in VSD. The access should be to the whole VSD database and we should be allowed to do any study that we choose. Obviously, the results of our studies will be subjected to peer-review as they were for our studies on VAERS when we submit them for publication. It is only by assuring free and complete access to the data by any scientific investigator that full public confidence in our vital vaccine programs can be fully restored.

[Contact us to obtain copies of the exhibits.]

Mr. BURTON. I think Dr. Weldon has a quick question for you, Dr. Geier.

Mr. WELDON. I think you answered my question. Thimerosal was in single-dose RhoGAM injections?

Dr. GEIER. Yes. That's the only kind of RhoGAM injection I've ever seen; and I have bought it from several companies, and they're always single-dose. They come in a syringe, prefilled, and they contained, up until recently, a year or two ago, thimerosal.

Mr. BURTON. Thank you very much.

Dr. Geier, that was an excellent presentation, as well. We'll try to make sure, along with Dr. Baskin's, this gets to everybody. I'm going to send this to Secretary Thompson over at HHS. I hope I can convince him to watch this whole presentation.

Dr. Spitzer.

Dr. SPITZER. Thank you, Mr. Chairman.

In the interest of time, I will focus on the Danish study, as requested. There are somewhat related matters that I will go over a bit more quickly, but the main focus is on the Danish study, and the paper was the New England Journal paper appearing on November 7th, which itself focused primarily on MMR. And the hypothesis declared in the paper in the New England Journal was about a relationship and association between the vaccine and autism, simply expressed as that, by a Danish group, about which I'll say a bit more in a moment.

So, in evaluating the hypothesis that MMR vaccination and autism are associated, they came through enlightened policy of the Danish Government to link data bases of the—data bases I have on the projection here, which are, from my experience of the Saskatchewan data base, perhaps one of the best, to look at relationships between disorders and risk factors, however they might be exposed, properly done.

I'll emphasize that the linkage was with computerized data bases. Also, I will mention it again, they were created for other purposes, and they were well linked.

Madsen has a good reputation in Europe. I worked in Europe for 4 years on epidemiologic studies and know their work by reputation. I have not met Madsen or any of the coinvestigators. I have no interest one way or another in terms of that team.

It was sponsored and funded by the Centers for Disease Control and Prevention. I'll have more to say about that.

Let me read the conclusion from the abstract, which is very similar to the conclusion later in discussion of the paper: "this study provides strong evidence against the hypothesis that MMR vaccination causes autism," and the emphasis is mine.

The category of the study, it is a cohort study which was, as a cohort study, well done, the followup being from January 1991 to December 1998, 8 years, and there were over 500,000 children in the cohort, 440 having received MMR, or 82 percent; and they translated this to personal years because of the difference in time of followup of different children. That was appropriate to do; it was the right thing to do in what was a dynamic cohort—that is, opposed to fixed. You don't start with, say, 100,000 children today and follow them together in the future.

The children were introduced to the cohort as they were born, we call it a dynamic, and followed forward in time to determine whether the outcome of interest, in this case, several subgroups of—several manifestations of autism appeared or not during that period of time, although the followup went on for one more year; and then I just show here how—visually how that happens.

Now, this was a major strategic advance in epidemiology. You have heard me say here before words to the effect that most, if not all, of the epidemiology until now has been clearly shoddy. People think that because the discipline is in adolescents, maybe infancy, you can afford to be shoddy. In fact, you should pursue as high a standard as possible. And it's also the first epidemiological study published to be adequately controlled, an adequately controlled observational study.

An important attribute of linked national data bases, or provincial ones like Saskatchewan, is that there is no selection bias. This is especially true in Denmark where well in excess of 97 percent of the people and the children of the country, however they entered, by immigration or birth and so on, are there. It's not matter of representivity. They're all there. So there is no selection bias. That's very hard to accomplish in epidemiology when you don't have this advantage.

Now, unfortunately, the important strategic advance was not matched by some important, detailed methodological tactics in the execution of the study. That vitiates the strength of the authors' conclusions, which I found unusual considering what came out in the data, which I'll summarize in a moment, and in this presentation, I'll review some of the methodological problems without being exhaustive.

Let me share with you that much of what I have here is as a result of conversations of colleagues, some seniors, who have written to the New England Journal. There hasn't been enough time yet to accept the things, and I need to respect confidence. I myself have forfeited my letter because I think it's more important, more socially sensitive that it be presented here, but I cannot assume that of any colleague; and on one or two occasions that I have asked permission, it's been denied and understandably so. They might get promoted. I can't.

Now, the key result to be published here, which leads to public statements of reassurance from authorities not only in this country, but in Europe and elsewhere, is a relative risk of 0.92 with confidence interval there, which shows no significance, as it wouldn't if there is no difference—that's for autistic disorders, one of the two major subgroups here; and for other autistic spectrum disorders, 0.83, again with that confidence interval.

And unlike the CDC study that I discussed at an earlier meeting, Mr. Chairman, the power here is high. Remember, it's only 12 percent in Davis' study. Here, it's 80 percent to detect an authorization of 1.5, and I remind you that in OR, an observation of one shows no association, and the key results we have here with the confidence intervals overlap 1, and there's the power which is quite adequate. In fact, it's superior. You don't often see that high a power obtained.

It's curious. They never give it to you. You have to calculate it yourself, but that's the way it is.

Now, going to some of the more detailed problems—and if I went into everything I'd be here for 2 hours, Mr. Chairman; I wouldn't be too popular even with you. But the first thing I'd like to say and perhaps the most important point, that of the numerator, the affected cases here, only 13 percent were reviewed. That is very inadequate, especially if done for validity purposes, just for validity.

To fail to examine all the records among the 787 children in the numerators of the cohort, or 738 in Table 2, that are similar, and without using a clinical and epidemiologic and large statistical multidisciplinary approach, it leaves the project wide open to errors and misclassification.

They said that because it was validity and it's a psychiatric diagnosis in Denmark, they had to use psychiatrists. Well, that's the last reason I'd use psychiatrists. I want validation from other health professionals, appropriately involved clinically and otherwise in the situation.

If they say it was too much work, in a self-selected group of affected children in Britain, with which I have been working with Professor Leary, among others, and so on, we did nearly 500 children, 493 children, looked at their lifetime histories with seven colleagues, including psychologists and pediatricians and so on, in about a month.

In later collaboration, also of 62 of the involved, for reasons they became involved in laboratory study, one-third of them, 28, or 45 percent, which is artificially high; but nevertheless, we could clearly show they were regressive; and with a bias against it, because we forced the situation where you waited 30 days—not just 3 or 4, as can happen, but we took 30 days to be very conservative—and it was in that little period we call them "unconfirmed."

The probable proportion in general populations—we could get it in Denmark, but they didn't do it—is between 10 and 15 percent.

Now, my questions are, were clinical psychologists and other clinicians involved in the Danish exercise? Was noncaseness validated, the controls? Was there a definition of zero time for any manifestation? They talk about diagnoses, but zero time is when you first observe by a competent clinician the signs or symptoms related to the condition. It may take years for you to get the diagnosis, especially by a psychiatrist, and the average in our studies was about 2.2. Other British studies go up to averages of about 5.2.

Regressive autism, I asked the question, but I don't think it was demarcated and whether there would be prolonged exposure to MMR when they were doing the review.

Now, I'm going to make the most important point of the presentation, in case you need to cut me short a little bit down the line. Assume hypothetically—and I'm doing everything conservative—that there is a vulnerability to MMR-induced disease in a subgroup of 10 percent of the autistic cases.

Mr. BURTON. Should this be a new slide?

Dr. SPITZER. Sorry.

So we assumed that there's 10 percent and we assume further that in the main autism group, 80 percent had been vaccinated, which is similar to the 82 percent we've seen in the paper and 95 percent vaccinated in the subgroup of autistics, all of it being plausible. And I stress this is hypothetical.

Now, if you did a nested case control study within these cohorts, which I'll explain in a minute, and did that design in those Danish cohorts, the odds ratio for MMR in that subgroup of 10 percent would be 4.17, which is appreciably high for preventive or therapeutic medicine in pharmacal epidemiology.

Now, combining all the autistics, the OR becomes 0.97, so that the 90 percent mask what's happening in that 10 percent.

Here I show briefly—this will be distributed—how the calculations will be done. And I assume—and I stress it's hypothetical. That's why we don't give confidence intervals. It would be contrived.

Now, is 10 percent trivial? Conservatively, very conservatively, perhaps this is half. Ten percent would represent approximately 50,000 children in the United States alone, perhaps a little less, with the yearly burden of one point—I'm sorry, with a lifetime burden, it would be of 1.25 billion for just that 10 percent. It isn't trivial. And as a public health doctor, I hope MMR can be ruled out.

There are those that say I am biased, and I will admit it, but let me tell you that my bias as a public health doctor is a profound desire that we can exonerate this effective vaccine, because it is one of the most effective interventions for important problems we have. But the failure to demonstrate safety so far means I cannot recommend it, even after the Danish study, for my own grandchildren.

So there is the—there is the trivial figure for the 10 percent.

Next slide. Two slides—another slide, I'm sorry. Now, next slide.

At the core of the methods problem is that the workers described a very important subgroup in the introduction of their paper but did not examine it specifically. They did not or could not test the most relevant hypothesis as proposed by Wakefield. In other words, they were looking for a question to be appropriate for the question they were putting and ignoring what Wakefield and others have published over the last few years from clinical and laboratory and not epidemiology.

Next slide.

Now, there are also analytic issues, and these are the ones that I am reticent to give too much—you will see it in the literature within days or, at most, weeks. Now, one strength here is that Madsen and her colleagues used person years. That's what you do in a dynamic cohort situation. I've seen it criticized, and I don't understand it because that's a strength. However, they had allocation of cases to subcohorts of exposed and nonexposed which are difficult to understand. That's one of the two examples that I gave. There is an unusual distribution of ages in the cohorts to which you alluded to, Dr. Geier, and they have problems with measurement of clinical phenomena, and their censoring rules are surprising or are inappropriate.

These are just five or six of the statistical issues over and above that main issue of failing to protect against hiding a phenomenon in a subgroup by looking at the 90 percent, if you wish.

Next slide.

So the questions I have first is, why did Madsen and IOM do an adjustment to the subcohort that removed six autistic and a total of 13 cases of progressive developmental disorder cases from the vaccinated subcohort and then place them in the unvaccinated one? This single adjustment reduces relative risks of autism due to MMR vaccination by 17 percent, from 1.26 to 1.09.

Next slide.

Why did Madsen not simply exclude all cases involving earlier, that is, nonregressive, diagnosis of autism? If they had removed all cases diagnosed before 2 years of age from both subcohorts, the relative risk would have risen from 1.26 to 1.28.

Next slide.

Now, another problem is difficult to understand. I'm not saying they are wrong, but I still haven't quite figured out what they did and why and how they adjust it. To age cohorts coming close to the end of the study or the end of followup, we have an average inception of the disease. It's about 3 years. If you only follow them for a year and a half, you are going to miss an awful lot of autistic cases among those exposed. So the censoring is difficult to understand, how they adjusted for it. I'm still in the process of figuring out and may well write an article on that with colleagues in the relatively near future.

Next slide.

Now, the classical problem of computerized data bases as they had, as we had in Saskatchewan, and I did a big study on beta agonists in Saskatchewan in—almost exactly 10 years ago, published in the New England Journal, the most cited paper in the literature that year. These data bases can and are useful, but there the data are gathered for other purposes, and when you go into those data bases, sometimes you just cannot get the data you need because it was never gathered or it was never archived. That may almost certainly be the case here, and certainly variables could not be considered.

There has been very, I would say, wise discussion of mercury and the implications a few moments ago. There was nothing about mercury in all of this and nothing mentioned.

Next slide.

I think we will skip this. This has to do with what I have from Wakefield in the literature, the fact that this is multifactorial. It involves interactions between potentially enabling factors, triggering factors such as mercury and MMR working in concert, subgroups genetically. You know, I don't know much about genetics, and I don't know—I don't—can't appreciate well how far we have gotten there, but I really hope we never discourage the pursuit of genetic information because it's likely to be an interactive, multifactorial profile which we don't understand yet.

Next slide.

Now, the fourth issue is research management tactics, which refers to some of the issues that you directly or indirectly mentioned earlier, Mr. Chairman, you and some of the colleagues. The concerns are about the process of funding, the interaction of sponsors with protocol formulation and approval, compliance with protocol, the role of the investigators vis-a-vis sponsors in the actual conduct of search and the input of the CDC epidemiologist in the preparation of the report with its conclusions. Now, sponsors should stay out of it except through clear, ethical accountability patterns. Sponsors should not be involved in the research.

Was there a protocol?

Next slide. Next slide, please.

Was there a protocol? Who approved it? Were there any changes in the protocol? Who approved the changes? Who monitored the work in progress? Who approved the final report? Was there a scientific advisory board? What exactly was the role of the CD and its professionals? That I don't know, and it's not in published literature, and it's not been the appropriate thing, for now, for me to approach Dr. Madsen.

Next slide.

Now, I would like to point very quickly to epidemiologic research priorities based on computerized data bases. The Danish one is excellent, it really is, for that kind of data source. And we don't have it in the United States. We only have it in Saskatchewan in Canada, maybe to a lesser extent in Quebec, a few other places, perhaps Sweden. But in Sweden the confidentiality is so high that they destroy your letters before they read them.

As I said, heavy metals and the developing immune system, all those issues, were not touched on for reasons I said.

Forgive me for going on ahead. Next slide. Next slide.

Likewise, we have heard here, and earlier testimony which I heard, synergistic adverse effects upon the immune system of susceptible children could not be studied here. The triggering phenomenon couldn't be studied in any manifestation of autism.

Next slide.

There is no mention of heavy metal as a likely multifactorial causal association. And it's not the fault of the investigators. I don't want us to go away and thinking badly of Dr. Madsen and her colleagues. They are good scientists. We don't know the pressures they had upon them, whether yes or no, from outside agencies. But this cannot be done with the Danish link data bases, as good as they are. It just can't be done.

Mr. BURTON. Doctor, sir, are you near——

Dr. SPITZER. I'm almost—2 minutes or so.

Mr. BURTON. Thank you, sir.

Dr. SPITZER. Next slide.

Now, it's my view and that of others that the Madsen group should replicate, extend, and perform complementary designs of the recent work. One should also explore whether it is feasible to do the same in Saskatchewan, Canada.

Next slide.

The hallmark of science is replication, verification, and corroboration. One study proves nothing. In any of these national preventional data bases, one can do cohort studies that are extensions and corroborations and—but the methods must be declared for analysis in advance. And unless the case control study goes into this representative two subcohorts, takes all the cases as cases and takes the probability representative sample of the controls as the controls, and then you have all the advantages of both cohort and case control in one study and at about a tenth of the cost, for that matter.

Next slide.

Now, there must be total transparency, considering the things that I've heard from distinguished members from both parties of the committee. There must be a scientific advisory board monitoring all phases, especially protocol changes in progress, proposed publications. The majority should be epidemiologists and biostatisticians. Ethics and conflicts of interest for reasons that are self-evident and may ultimately—should be under surveillance, perhaps by a community advisory board as we did in Alberta.

And the main protocol should be published in advance. We should be able to critique that protocol in the peer-reviewed literature. In major studies, that's what my group at McGill do and what many groups in Europe are doing as well, even in North America.

Next slide.

A significant first step has been taken in epidemiology. It is imperative that the whole feasible road of research be taken. One study proves or disproves nothing in any field, or two, if you take the lines, that one that you described.

Thank you for your attention.

Mr. BURTON. Thank you, Dr. Spitzer. We appreciate your comments as well.

[The prepared statement of Dr. Spitzer follows:]

Testimony of Walter O. Spitzer, M.D., M.P.H., F.R.C.P.C.

Emertius Professor of Epidemilogy and Past Chairman, Faculty of Medicine, McGill University

Emeritus Editor, Journal of Clinical Epidemiology

Member, Institute of Medicine, U.S.A.

The paper, "A population-based study of measles, mumps, and rubella vaccination and autism" (Slide 3) published on November 7, 2002 describing a very good national data linkage based upon which a cohort study was done. It was sponsored and possibly supervised by the Centers for Disease Control and Prevention of the United States of America. A group led by KM Madsen with a good reputation in Europe did the study. The main conclusion from the study is "This study provides evidence against the hypothesis that MMR vaccination causes autism." (emphasis mine). The study is a major improvement over all earlier epidemiologic investigation due to an appropriate controlled design. Unfortunately, the strategic advance was not matched by some important methodological tactics in the execution of the study. That vitiates the strength of the authors' conclusions. Without being exhaustive.this presentation reviews some of the methodological problems

A very important attribute of the linked Danish national databases was that nthere was no selection bias, the curse of almost all observational epidemiological research. The key result published is an odds ratio of 0.92 for autistic disorders which fails to attain statistical significance as expected but with good power of 0.80 for an OR of 1.5.

The main objection is that the apparently reassuring finding it almost certainly misleading if you consider that autism is likely to be caused multifactorially and that only a small subset of autistic patients may have been affected by MMR. For instance, hypothetically, if only one subset had been identified where 10% of all autistics were affected by the MMR vaccination, the OR would be 4.14 which is high for that 10% subset. But it is not a trivial subset. Conservatively, in the United States alone, 10% would result in a financial burden of suffering of 1.25 billion dollars in for the lifetime of the children in direct expenditures alone.

Further, there were several analytic shortcomings and problems. Censoring was done inappropriately particularly for the later birth cohorts. The age distribution of the children is unusual and questionable as the basis for standardization. Some important variables could not be examined at all.

As of December of 2002 I have important unanswered questions on the study management particularly the role of the CDC .

Madsen and perhaps Canadian investigators need to replicate, verify and corroborate the initial Danish study. An important step forward has been taken. But one study does not prove or disprove any hypothesis definitely. The road of research needs to be followed. Excellent research standards need to be matched to transparent and ethical standards of management in exploring the causes of the baffling epidemic of autism.

Mr. BURTON. I think I will let Dr. Weldon start off. Doctor, would you have any questions?

Mr. WELDON. Yes, Mr. Chairman. I have a question for Dr. Geier.

You said the CDC or the FDA has the data as to which manufacturers produce which vaccines that contain thimerosal and which ones don't. And the VAERS data shows that some of them have a higher incidence of these neurodevelopmental disorders, and—but you just can't disclose that? Is that correct?

Dr. GEIER. Yeah. There are three levels of denominators. One level is, how many doses of each type of vaccine were made per year? Which we have and can disclose, although that seems to be not generally available, but we have managed to get it.

The second one is broken down by company, which we have under agreement that we not disclose which company. So we can do a study like the one I presented and compare one with and one without, but I couldn't say such and such a company makes a vaccine and another company makes a vaccine, and the first company is five times worse than the second company.

And then the third level that they also have—and this is all published by them if they have it, is that they have the number of doses per lot number. So with that information you could investigate the possibility of a bad lot. I looked in my VAERS data, and I find some lots that have far more reported reactions than others, but I don't know how big the lots were. If I knew how big the lots were, I could tell you, yes, there was a bad lot of particular vaccine made in such and such a year or, no, there wasn't. And that information I've been unable to get with or without any agreements.

Mr. WELDON. So what you are saying is if it is an average-sized lot but there's a higher incidence of side effects——

Dr. GEIER. Well, I don't know. I mean, let's say I look at two lots, and one of them has 100,000 reactions and one of them has 10,000 reactions. It could be that the 100,000 was a 10 times bigger lot. If I average them, that's not valid. I have to know. And they know exactly how many doses were in each lot. And if they release that, we could look lot by lot through the VAERS data and say, well, there was a bad lot. Boy, it had 20 times—and we could do statistics to see whether it was just by random choice or chance or whether it was real that a particularly bad lot was made.

There has been a lot of literature on bad lots. In fact, in the 1980's the FDA used to keep a list called the "hot lot" list, and they also had trouble getting the numbers. But they have the numbers now to do it, and they won't release these to any scientists, and they won't allow people to discuss which vaccine company makes a worst vaccine when they're two of the same vaccine made by the same company, and I think consumers are entitled to that kind of information. It's sort of like, you know, we get an automobile crash test and you find, gee, one car is a lot safer than the other when it runs into a wall, but we are not going to tell you which kind of car. Well, they tell us which kind of car, but they won't tell us which vaccine producer. They won't allow it to be released which vaccine producer makes a safer vaccine. And I think with our children and our lives it's critical that we have that information.

Mr. WELDON. Dr. Spitzer, I always find it very interesting to hear you speak. It's frequently a little hard to follow, though, not being a biostatistician or an epidemiologist, so I just want to make sure I understand you correctly. You said the Danish study, the Madsen study, is a good study. But is what I said in my introductory remarks accurate, that it did not—is it the case that if MMR was causing the majority cases of autism, that the study is good, but if it's causing a percentage less than 50 percent, then the study is not valid? Is that what you were basically saying?

Dr. SPITZER. Well, what I would like to stress is that the Madsen study in a sense broke a barrier in being the first properly controlled epidemiological study ever done and new avenues which can be followed and also had the advantage of an extraordinarily good data base with the disadvantages——

Mr. WELDON. And I understood all that.

Dr. SPITZER. Now, what I'm saying is, they just didn't go far enough, first of all, with inadequate evaluation of the cases, both in terms of a small sample and in terms of how much within each case was looked at. We don't have the details of that.

And, second, I'm just saying they cannot rule out with the decisiveness that they imply, they cannot rule out an association. They can for the totality, but they can't say there is no subgroup that conceivably could be affected.

Mr. WELDON. So is it correct——

Dr. SPITZER. And so that's—it just didn't go far enough, even though it's a major advance in the study of autism epidemiologically in the last decade.

Mr. WELDON. Is it correct to read it and interpret that MMR does not cause the bulk of autism in Denmark, but it may cause—it could cause——

Dr. SPITZER. You can infer that if you take them as a totality and look at them that way. It's not detectable should it be happening in a subgroup.

Mr. WELDON. But if MMR is causing a percentage—let's say a percentage well below 50 percent, then that study didn't answer that question——

Dr. SPITZER. No.

Mr. WELDON [continuing]. Correct? OK.

Mr. BURTON. Can I followup on that, please? Would the gentleman yield?

Mr. WELDON. I would be happy to yield.

Mr. BURTON. In layman's terms, so that everybody understands, you are saying that it could cause 10 percent, 20 percent of the autism cases, 30 percent. Is that right?

Dr. SPITZER. When you get up to 30 percent, it's—but 20 percent or below is a concern.

Mr. BURTON. Well, see, that's something that a lot of us—you went right over our heads with all those statistics. But you are saying that it's possible that 20 percent of the autistic cases could be as a result of the MMR vaccine?

Dr. SPITZER. Yes, and cannot be ruled out by this study.

Mr. BURTON. Thank you.

Dr. SPITZER. I'd use the figure 10 percent to be conservative rather than 20, although it could be 20. But 10 percent is what we tested hypothetically and I'd like to speak to.

Mr. BURTON. Well, 10 percent is still a considerable number of children.

Mr. WELDON. Dr. Baskin, you are a clinician, I understand. Have you looked at the research data done by a Dr. Wakefield from England on the issue of MMR and autism? Are you familiar with that at all?

Dr. BASKIN. Yes, I'm familiar with that. I've actually met Dr. Wakefield and conversed with him.

Mr. WELDON. OK. One of the things that I have been very concerned about since I've been working with the chairman on this issue, and it's about 3 years now, I think this is now the third epidemiologic study. There were two out of England and then there was this—maybe it's the fourth one. I think there was a U.S. study, if I'm not mistaken.

Dr. SPITZER. There is the Finnish study as well.

Mr. WELDON. OK. But nobody has made an attempt to duplicate a clinical study like the original Wakefield research. And can you honestly refute Dr. Wakefield's clinical data with all these epidemiologic studies, particularly in light of the conversation I just had with Dr. Spitzer, that the study only—the best study we've had so far can only be used to say that MMR does not cause all autism cases in Denmark and that the study does not exclude the possibility that MMR is causing a percentage of them?

Dr. BASKIN. The answer is, no, I can't refute that. While thimerosal is my major research base as a clinician, and after conversations with Dr. Wakefield, one of his great concerns is regressive autism, the fact the child starts out normal and then gets worse, and another one of his great concerns is the second shot, none of these studies have actually looked at these subgroups in any detail.

Mr. WELDON. I have some more questions, but I would like to yield back to the chairman for the moment.

Mr. BURTON. Thank you.

Let me start with you, Dr. Baskin, and you, Dr. Geier. Because thimerosal—although MMR is a very important issue as well and important to me, I am interested in the thimerosal issue because it has been given to literally millions of people since the 1930's, and it's been given in more and more greater quantities in recent years because of the number of vaccinations involved. Do you personally believe from your studies that the mercury is a contributing factor to the cases of autism we have in this country?

Dr. BASKIN. Yes.

Mr. BURTON. Do you think it's a large contributing factor, or do you have any percentages? I mean, I know this is a tough question and everything, but you have done a lot of research.

Dr. BASKIN. I think it's hard to look at a percentage. I think that, as NIH is focusing on, there is probably an environment gene interaction. In other words, a lot of children get the injection and don't become autistic, and so there must be something specific or different about the way a certain subgroup of children are able to handle toxins which, as I alluded to earlier, is known for other toxins. I mean, that is not a foreign concept. I don't think we yet know the answer to that.

I think that one of the striking things is over the years at NIH and NICHD the idea of regressive autism was not well accepted. It was sort of originally preached that you were sort of autistic from birth and actually there weren't that many children who have regressive autism. But the NIH with good data and with good science has actually reversed its position quite a bit on that, and this group seems to be increasing. So up to somewhere between 30 and 40 percent of children in very conservative studies seem to have this regressive autism. In other words, it doesn't seem like they are starting out abnormal. Something happens to them, and they backslide.

So I think if you want to take a conservative estimate and you want to take those conservative numbers, because there are other studies that say 60, 70 percent of autism is regressive, I think that it's a very good chance it's more likely than not that it contributes or causes autism in about 40 percent of children who are autistic.

Mr. BURTON. Would you say that a child like my grandson who got nine shots in 1 day, seven of which contained thimerosal, would you say that they had a greater risk of getting a neurologic—creating a neurological problem like autism than——

Dr. BASKIN. Yeah, absolutely. I didn't touch on that. I tried to be very conservative with my analysis. But, as you pointed out, these EPA guidelines are a small amount per day. These kids are getting an enormous amount all at once. And you say—you could say you could average the amount of a lethal injection over your lifetime and say, well, you never in any 1 day got a lethal dose. The only trouble, you'd be dead and 6 feet under the ground. So, yes. I mean, those are the most concerning cases, children who were OK, who got worse, and whose parents can link this to a single or a set of—a serial set of exposures to mercury. And that sounds like the absolute typical case that we would be most concerned about.

Mr. BURTON. Dr. Geier, I think you indicated that in some cases kids are getting 100 times the amount of mercury that would be tolerable at one time.

Dr. GEIER. Yes. In fact, some of those calculations are over 100 times.

Mr. BURTON. So a child that got multiple vaccines in 1 day could conceivably be getting more than 100 times the amount, according to EPA, that's a tolerable level of mercury in one fell swoop?

Dr. GEIER. Yes. And their levels are actually conservative, because they meant by ingestion, not by injection. So their studies were not usually by injection.

Mr. BURTON. So the injection would be actually——

Dr. GEIER. It's worse.

Mr. BURTON [continuing]. Worse, much more lethal, so to speak.

Dr. GEIER. Yeah. I mean, there is no question that these children are overdosed.

Mr. BURTON. Would either one of you take nine shots in 1 day, knowing that seven of them contained mercury, at the same time? And—or would you allow that to happen to your kids or grandkids, whether they are healthy or not?

Dr. BASKIN. You know, a mercury thermometer broke in my house, and I cleared everybody out of the house and went to my lab and got these really bioresistant gloves, and cleared it up like a toxic spill.

No, of course not. It's a really bad toxin.

Dr. GEIER. I wouldn't. And I had a different situation. I run a laboratory that does chromosome analysis, and we had a mercury vapor bulb break. And we were located near the NIH, and we cleared the building and had the NIH guys come in with full body suits to clean out the area.

Dr. BASKIN. And I think we've dramatically underestimated what's been in the literature for the entire last century, that this is a highly toxic compound. The more we look into it, the worse it gets.

Mr. BURTON. And it shouldn't be injected into human beings.

Dr. BASKIN. Absolutely not.

Mr. BURTON. But one of the things—one other thing I want to talk about, and this is not related to my personal problems, I hope. And that is that older people are coming down with Alzheimer's at a more rapid rate than in the past. Do you attribute that in any way to the levels of mercury that they are ingesting, either through their amalgams in their mouth or the vaccinations that they are getting or the food that they are eating that contain mercury?

Dr. BASKIN. I think that's a less well-studied area. But this work that you described, which I was aware of, of the fact that as these cells die from mercury they form these kind of plaques and tangles like we see in Alzheimer's disease is very intriguing and certainly suggests this may well be a contributing factor.

Mr. BURTON. And should be studied.

Dr. BASKIN. Absolutely should be studied.

Mr. BURTON. Dr. Geier.

Dr. GEIER. I agree. I think it's well-studied, could be studied, but is very plausible.

Mr. BURTON. I don't want to alarm everybody in the United States, but the Members of Congress have been getting flu vaccines that contain thimerosal for several years. And I want you to know that I don't think that's one of the reasons we have made bad decisions up here, although somebody might ask that question.

Dr. Weldon, do you have any more questions of this panel?

Mr. WELDON. Yeah. I have a couple of questions for Dr. Baskin about ethyl mercury versus methyl mercury. I have had some people say that data on methyl mercury is fairly good, but we don't have good data on ethyl mercury. I take it from your testimony there is actually quite a bit of data on ethyl mercury and that it's as toxic as methyl mercury.

Dr. BASKIN. There is more data, more and more data on ethyl mercury. The cells that I showed you dying in cell culture are dying from ethyl mercury. Those are human frontal brain cells. You know, there has been a debate about, well, ethyl versus methyl. But from a chemical point of view, most chemical compounds that are ethyl penetrate into cells better than methyl. Cells have a membrane on them, and the membrane is made of lipids, fats. And ethyl as a chemical compound pierces fat and penetrates fat much better than methyl. And so, you know, when I've began to work with some of the Ph.D.s in my laboratory and discuss this, everyone said, oh, gosh, you know, we've got to adjust for ethyl because it's going to be worse; the levels are going to be much higher in the cells. So, I mean, I think at best they're equal, but it's probably highly likely that they are worse. And some of the results that we are seeing in cell culture would support that.

Mr. WELDON. Now, you said several times in your testimony that uptake in the brain is probably much higher than in other tissues. What do you base that statement on?

Dr. BASKIN. Well, the literature on methyl mercury is much better than ethyl on this issue. And if you look at the studies, the brain is 2 percent of the body weight but took 10 percent of the exposure. So that's a fivefold preferential update.

Mr. WELDON. This was based on people who died?

Dr. BASKIN. Right. And also on animal studies, both.

Mr. WELDON. Animal studies? So the brain—what did they do——

Dr. BASKIN. The brain seems to take five times more the exposure than it should. In other words, if you assume that you give methyl mercury and it goes everywhere in the body equally——

Mr. WELDON. You should get the same level.

Dr. BASKIN [continuing]. You should get the same level everywhere. But the brain takes five times as much as it should have.

Mr. WELDON. And that was based on methyl mercury?

Dr. BASKIN. Methyl mercury. Correct.

Mr. WELDON. The Lancet study, only 40 infants. You agree that's much too small a sample size to really make any conclusions?

Dr. BASKIN. Right. I mean, there are a number of problems with the Lancet studies as I mentioned. But certainly, if the disease occurs in one in 150 children and you only test 40, you may miss that child, very easily miss the child who had the problem, or at best maybe only catch one. Not to mention the other things that have been discussed by several of the panel, the most significant one being they drew the blood much too late. They drew the blood days to weeks later, whereas we know the peak level of methyl mercury——

Mr. WELDON. Three to 28 days.

Dr. BASKIN [continuing]. Occur within hours, within 24 hours; yet they drew the blood up to 27 days later. As a matter of fact, to me it's very worrisome. They are still finding some mercury in the blood that far out. It should—you know, you would think it might be gone.

Mr. WELDON. Is there any——

Mr. BURTON. Would the gentleman yield? Would that be the reason that some families see a very, very rapid change in their children shortly after these vaccinations are given in large numbers? For instance, in our family it was just a matter of a couple days and—boom.

Dr. BASKIN. Correct. All of the data on both methyl and ethyl mercury suggests that the peak level—in other words, the highest level in the blood—is either achieved within hours or at least within 24 hours. So that's—and, again, if it gets in the blood, the blood goes to the brain. We know it has a preferential tendency to be sucked into the brain or to cross into the brain in excess, and so you would expect to see something fairly quickly. As a matter of fact, if somebody said 3 months later something happened, I would say that's probably not related.

Mr. BURTON. Can I followup with one question here?

Mr. WELDON. Sure.

Mr. BURTON. In animal studies, as I understand it, the animals evidently didn't become ill for 14 days after the injection of the mercury. Are you familiar with that study?

Dr. BASKIN. It depends on which study you are talking about. There's a variety of different studies.

Mr. BURTON. Well, it's a rat study that was done in the 1950's by the Eli Lilly company. Are you familiar with that?

Dr. BASKIN. I'm not familiar with that particular study. But, you know, in general, remember that if you are doing studies on rats and mice, you have to have very sensitive behavioral screens. As long as they are getting up and eating, I mean, they might be acting weirdly and you wouldn't know it. So I—without knowing what study you're referring to, it would be hard for me to comment on it.

Mr. BURTON. Thank you.

Mr. WELDON. Is there any kinetic studies on the clearance of ethyl mercury that are available that could allow you to make conjectures as to what the peak levels might have been based on the blood levels that are available in the Lancet study? Or is that information not known?

Dr. BASKIN. It's known to a limited extent.

There's a study in pre-term infants that received vaccinations. So they—you know, by kind of people not thinking about it, their weight is very small and they receive the same dose, and so it was a very high level. And they looked at some of that data. But, frankly, there is not enough.

I think one of the points in the Lancet study is they drew all these complicated curves saying that they knew what the pharmacokinetics were, which refers that they knew how the drug was taken up, how it was absorbed, how it was distributed, but they never caught a peak level. And, of course, you can't even make a comment about pharmacokinetics unless you know the peak level.

So, I mean, I think the short answer is there is some—some data available but not enough.

Mr. WELDON. Dr. Geier, when this issue was first brought to my attention 3 years ago, I was very disturbed about the mercury issue. Then the CDC study that you referred to where you drew those curves came out; and, frankly, I was somewhat relieved with that data. Not being a scientist or an epidemiologist, I accepted it at face value. There was some initial data suggesting that some of the kids had language and speech development problems, and then they added more numbers and said that association went away. I'm very disturbed by these curves that you drew, though.

So you're saying that—I just want to make sure I understand you correctly—that when you plot out the data like that, you can actually do a calculation and it is statistically significant?

Dr. GEIER. Yes. When you—if you allow us to remove that greater than 62 point——

Mr. WELDON. Well, I want to ask you about that. You say it's got to be 75. Is that based on the immunization tables and the known amount of——

Dr. GEIER. Yes.

Mr. WELDON [continuing]. Thimerosal in there? So they couldn't have gotten 150 or 200. It had to be 75.

Dr. GEIER. Right. It had to be 75. And when you allow that point, then you have a curve-fitting program that tries to fit the best curve. And it tells you how well the curve fits to that, and it fits in greater than 95 percent to a logarithmic curve.

Mr. WELDON. Not being a scientist, I can't honestly—but I just know what it's like. You know, I'm going to get the CDC people in my office after all this is over, and I'm going to say, OK, how do you respond to all of this? And I don't think they are here today, right? They are not in the second panel, Mr. Chairman? Which I'm very disappointed by. But I would assume they are going to say that's not kosher, so to speak, what you did; that's not a valid scientific technique.

Dr. GEIER. No, I think they're going to be upset that we used their intermediate data before they added all these young children to dilute it out. And even when they diluted it out, by the way, it's still there. It just became more dilute. As far as, you know, doing the curve, I think they'd have to agree that, you know, if you analyze a single point and then you compare that to analysis of several points as they go up, you add more likelihood that it's significant. I mean, just intuitively, what's the odds that three go up in a row? I mean, just supposing something is random, forget about even how much they go up or even what shape they go up, the odds of three going up in a row are not so good if they were from a random subject.

So it's obvious that to intuitively that—but—and as well as mathematically that when you go to a kinetic curve like that, the curve can be significant even if each individual point is only, as I think they said, marginally significant. You get three marginally significant curves that fit like that, it becomes very significant.

But maybe Dr. Spitzer, who is our epidemiologist and mathematician, can comment on that.

Dr. SPITZER. Well, it's—trying to say it in nontechnical terms—but it is a finding that's being observed by appropriate rules of handling the data in the main. It's usually preferable that it be declared in advance, and that 75 that he said, not in the course of analysis and so on, but that this is not likely to happen by chance, at least at the 95 percent level, or chance alone. That's the basic principle. It's a finding where the role of chance has been excluded to the extent of 95 percent.

Mr. WELDON. I believe I understand. I could really go on much further, but I was just reminded we actually have a second panel, and we have been at it for 2½ hours, so I will yield back. I'm sorry, Mr. Burton.

Mr. BURTON. No, that's fine, Dr. Weldon. You ask more poignant questions than I, because you have that experience and background.

Before I recognize Congressman Green, who I believe is Dr. Baskin's Congressman—is that correct?

Dr. BASKIN. Yes.

Mr. BURTON. Is he a good one?

Dr. BASKIN. He is very good.

Mr. BURTON. OK. Well, I just thought I'd ask.

Dr. BASKIN. He is a good patient, too.

Mr. BURTON. That's unsolicited testimony.

Before I recognize him, let me just ask you one quick question here. Do you, all three of you, think that our health agencies have done enough in the research of this very, very important issue of the epidemic of autism?

Dr. BASKIN. My opinion is this: I think that the NIH now is galvanized and is doing more. And if, as I said earlier, if more funds could be set aside for this specific issue, they have the capability and the interest to do it.

Mr. BURTON. Have they in the past?

Dr. BASKIN. Not in the past, no, but I think they are now.

Mr. BURTON. So we have an epidemic, and up to this point they haven't been doing enough.

Dr. BASKIN. Right. I think so. I think so. But I think, to be fair to NIH, a lot of this information wasn't really made available; like I talked about agencies not talking to each other.

Mr. BURTON. What about CDC?

Dr. BASKIN. I think the CDC is not. The CDC, in my opinion, has been obstructionist.

Mr. BURTON. OK. How about the FDA?

Dr. BASKIN. The FDA, as they said in their own e-mails, I think have been asleep at the switch for decades.

Mr. BURTON. Asleep at the switch. OK. Dr. Geier.

Dr. GEIER. I think—it's Geier.

Mr. BURTON. Geier.

Dr. GEIER. I think that they've been asleep, and I think that we found that out when we did a midline search on thimerosal. There are over 1,500 articles listing problems with thimerosal. And that doesn't go back—the midline search goes back to 1967. Actually, the problem goes back farther than that. If there are 1,500 articles that are implying problems with thimerosal and the FDA and CDC knew that it was in the vaccines, something should have been done, more than just ignoring it.

Mr. BURTON. Thank you, Dr. Geier.

Dr. Spitzer.

Dr. SPITZER. Well, as I mentioned before, on this whole matter, particularly as it concerns MMR, I call myself a worried agnostic. If I, from the FDA or some of the sister major agencies around the world, could get assurances that we have the same quality information on safety of this product as we have on efficacy or effectiveness—and that is good—my worry would go down a bit, or go down quite a bit. It's gone a little bit down with the Danish studies. But that's what I have not been able to find, Mr. Chairman, is adequate, scientifically admissible evidence on the safety of the products as opposed to efficacy.

Mr. BURTON. And at this point you wouldn't give your grandkids the MMR vaccine?

Dr. SPITZER. Not yet. No. Not in the foreseeable future, I don't think.

Mr. BURTON. Thank you. Well, let me just end my comment here by saying that the FDA and CDC and our health agencies have an awful lot of questions that need to be answered. But the one thing they could do to make the situation a lot better is if they get on—get on with admitting there is a problem if there were 1,500 articles—and start really getting down to the business of studying this thing and devoting the amount of resources that are necessary to get the job done. And I want to thank you guys very much for your help.

And, with that, Congressman Green, it's good to have you with us.

Mr. GREEN. Mr. Chairman, I did serve on this committee three terms ago and I moved to the Energy and Commerce to deal with health care. It's interesting; I walked back in the office from a meeting and saw Dr. Baskin, who, one, is a great friend and great neurosurgeon, and I'm going to ask him to sign an affidavit that, yes, a Member of Congress does have a brain. But——

Mr. BURTON. Did you get a flu shot this year?

Mr. GREEN. I did get a flu shot in.

Mr. BURTON. Well, it has mercury in it.

Mr. GREEN. OK.

Mr. WELDON. You know, he has brain cells he's growing in his lab. I was wondering if he would sell some to Members of Congress.

Mr. GREEN. You know, we could use them. We could use them. But the issue—because we were just responding in our office to a letter of a family with a child with autism. And on my Subcommittee on Health Care, that our good doctor is also on, this is an issue. And I want to thank you for holding these hearings to help us as Members of Congress go further. But again, I just came in to say hello to my good friend Dr. Baskin.

Dr. BASKIN. Thank you.

Mr. BURTON. Before you leave, let me just say that——

Mr. GREEN. Thank you.

Mr. BURTON. Thank you. Before you leave, I just want to say that we have a bill that I've talked to Congressman Bilirakis, the chairman of your subcommittee about, that would go a long way toward helping solve the problem with the vaccine injury compensation fund, and I really would appreciate if you'd talk to him and take a look at that bill.

Mr. GREEN. OK. Glad to.

Mr. BURTON. Thank you very much.

Well, gentlemen, thank you very much. We have gone way beyond what we normally would, but I thought it was very important to let you really lay out the whole story. And with that, we will go to the next panel. And thank you for your service.

Mr. BURTON. The next panel is, we have the FDA and the NIH, Dr. Midthun, Dr. Foote, and Dr. Portier. Would you please come to the witness table?

Please stand up so I can swear you in, please.

[Witnesses sworn.]

Mr. BURTON. Dr. Midthun, do you have an opening statement?

Dr. MIDTHUN. Yes, I do.

Mr. BURTON. OK. You are recognized.

STATEMENTS OF KAREN MIDTHUN, M.D., DIRECTOR, OFFICE OF VACCINES RESEARCH AND REVIEW, FOOD AND DRUG ADMINISTRATION, ROCKVILLE, MD; STEPHEN FOOTE, PH.D., DIRECTOR, DIVISION OF NEUROSCIENCE AND BASIC BEHAVIORAL SCIENCE, NATIONAL INSTITUTE OF MENTAL HEALTH, BETHESDA, MD, ACCOMPANIED BY CHRISTOPHER PORTIER, PH.D., DIRECTOR, ENVIRONMENTAL TOXICOLOGY PROGRAM, NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES, BETHESDA, MD

Dr. MIDTHUN. Thank you.

Mr. Chairman and members of the committee, I am Dr. Karen Midthun, Director, Office of Vaccine Research and Review of the Center for Biologics Evaluation and Research at FDA.

Mr. Chairman, as a physician and a parent, I want to express to you, the members of this committee, and to parents and physicians that I appreciate the devastating effects of autism on children and their families. I am here to assure you that we are working diligently to help ensure that the vaccines we license for use in the United States are shown to be safe, pure, and potent. I appreciate the opportunity to participate in this hearing on autism and to respond to the committee's concerns regarding a potential link between vaccines and autism.

The Office of Vaccines regulates the investigation and licensure of vaccines. FDA's regulatory process for licensing vaccines has for decades served as a model for other countries. To date, the existing data do not demonstrate a causal relationship between vaccines and autism. Nonetheless, I want to assure this committee, the public, and especially parents, that FDA continues to take these issues seriously.

One concern that has been raised relates to the use of thimerosal, a mercury compound, as a preservative in some vaccines. FDA recognizes and supports the goal of reducing exposure to mercury from all sources. Consistent with this goal, FDA has encouraged manufacturers to develop new vaccines without thimerosal as a preservative and to remove or reduce the thimerosal content of existing licensed vaccines.

As required by section 413 of the FDA Modernization Act, FDA conducted a review of the use of thimerosal in childhood vaccines. Our review showed no evidence of harm caused by thimerosal used as a preservative in vaccines except for local hypersensitivity reactions. Of the U.S.-recommended childhood immunization schedule, the maximum cumulative exposure to mercury from thimerosal at the time of this review in 1999 was within acceptable limits for methyl mercury exposure set by FDA, the Agency for Toxic Substances and Disease Registry, and the World Health Organization. However, during the first 6 months of life, cumulative exposure to mercury could have exceeded the more conservative limits of the EPA in some cases, depending on the specific vaccine formulations used and the weight of the infant. Of note, all of these guidelines contain a safety margin and are meant as starting points for evaluation of mercury exposure, not absolute levels above which toxicity can be expected to occur.

The clinical significance of exceeding EPA's limits is not currently known. Nevertheless, reducing exposure to mercury from vaccines is warranted and achievable in principle in the United States because it is possible to replace multi-dose vials with single-dose vials which do not require preservative.

I am pleased to be able to report substantial progress in the effort to reduce thimerosal exposure from vaccines. Since early last year, all routinely recommended licensed pediatric vaccines manufactured for the U.S. market contain no thimerosal or contain only trace amounts of thimerosal in the final formulation. With the newly formulated vaccines, the maximum cumulative exposure from vaccines during the first 6 months of life is now less than 3 micrograms of mercury. This represents more than a 98 percent reduction from the previous maximum cumulative exposure of 187.5 micrograms of mercury from vaccines.

In addition to the initiatives taken with regard to routinely recommended childhood vaccines, FDA has also worked with manufacturers to facilitate the removal or reduction of thimerosal from other vaccines. Two of the three influenza virus vaccines are now available in a formulation that contains only trace thimerosal. The manufacturer of the third influenza virus vaccine has announced that it will not manufacture this vaccine after this year.

In 2001, the Institute of Medicine's Immunizations Safety Review Committee focused on a potential relationship between thimerosal use in vaccines and neurodevelopmental disorders. The Institute of Medicine concluded that the evidence is inadequate to either accept or reject a causal relationship between thimerosal exposure from childhood vaccines and the neurodevelopmental disorders of autism, attention deficit, hyperactivity disorder, and speech or language delay.

Additional studies are needed to establish or reject a causal relationship, and we concur with that.

The committee believes that the effort to remove thimerosal from vaccines was a prudent measure in support of the public health goal to reduce mercury exposure of infants and children as much as possible. In an effort to better characterize the potential toxicity that could have accompanied an exposure to thimerosal from vaccines, FDA nominated thimerosal to the National Toxicology Program for further study. The nomination was accepted by the review committee earlier this year.

Reports of developmental delay following vaccination have been submitted to the Vaccine Adverse Event Reporting System, commonly referred to as VAERS. Although VAERS reports usually cannot establish a causal relationship between a vaccine and an adverse outcome, further study of these reports can sometimes provide important clues and suggest directions for further research. FDA takes these reports seriously and is conducting a followup study of VAERS reports of autism. Also, FDA is pursuing promising research involving the characterization and development of an animal model to study general biological principles for autism.

By looking at ways to improve the safety of vaccines, we must keep in mind that childhood vaccines have contributed to a significant reduction of vaccine-preventable diseases, including polio, measles, and whooping cough. It is rare for American children to experience the devastating effects of vaccine-preventable illness. Although they provide a great public health benefit, vaccines, like all medical products, are not risk free, and FDA is committed to continuing its efforts to reduce these risks whenever possible.

In conclusion, FDA continues to work diligently with manufacturers to eliminate or reduce exposure to mercury from thimerosal and vaccines. Since early last year, all routinely recommended licensed pediatric vaccines manufactured for the U.S. market contain no thimerosal or contain only trace amounts of thimerosal in the final formulation. Although no causal relationship between vaccines and autism has been established, FDA, along with other health and human services agencies, continues to pursue and support research activities to increase our understanding of any potential relationship between vaccines and neurodevelopment disorders.

Although the prevention of disease through the use of vaccines is a tremendous public health accomplishment, there is more work to be done. I assure you that the Office of Vaccines and FDA will continue to make regulatory decisions and recommendations regarding vaccines based on the best scientific evidence to protect the public health.

Mr. Chairman, I appreciate the committee's interest in this area, and look forward to continuing to work with you in the future. Thank you.

[The prepared statement of Dr. Midthun follows:]

Testimony
Before the Committee on Government Reform
United States House of Representatives

FDA's Ongoing Response to the Issue of Vaccines and Autism

Statement of

Karen Midthun, M.D.

Director,
Office of Vaccine Research and Review,
Center for Biologics Evaluation and Research,
Food and Drug Administration,
U.S. Department of Health and Human Services

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Introduction

Mr. Chairman and Members of the Committee, I am Dr. Karen Midthun, Director, Office of Vaccines Research and Review (OVRR), Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration (FDA or the Agency). CBER regulates the development and licensure of vaccines. We appreciate the opportunity to participate in this hearing on autism and to respond to the Committee's concerns regarding a potential link between vaccines and autism. It is important to note that to date, the existing data do not demonstrate or even suggest a causal relationship between vaccines and autism. Nevertheless, we want to assure this Committee, the public and, especially the parents that are here today, that FDA takes these concerns very seriously. We want to explain FDA's ongoing efforts in response to the issue of vaccines and autism.

Childhood vaccines have contributed to a significant reduction of vaccine-preventable diseases (e.g., polio, measles, and whooping cough). In fact, vaccine-preventable infectious diseases are at an all-time low and now it is rare for American children to experience the devastating effects of these illnesses. Before vaccines were routinely administered, there were over 175,000 cases of diphtheria annually (1920-22), over 147,000 cases of pertussis (1922-25), and over 503,000 cases of measles (1951-54) reported in the United States. These diseases have essentially disappeared in countries with high vaccination coverage, such as the U.S. Prior to the introduction of an infant vaccine in 1985, an estimated 20,000 cases of invasive *Haemophilus* *influenzae* type b (Hib) disease, primarily meningitis, occurred annually in the U.S. Now, because of vaccination, the number of cases of invasive Hib disease has decreased by more than 98 percent. All of the diseases mentioned above were associated with significant mortality and morbidity. Nevertheless, we need to follow up on any safety concerns related to vaccines.

Background

Like all products regulated by FDA, vaccines undergo a rigorous review of laboratory and clinical data by highly trained scientists and clinicians to help ensure the safety, purity, and potency of these products. From an FDA regulatory perspective, there are four stages in vaccine development: the pre-investigational new drug (IND) stage (before the product is used in people), the IND stage (where human use occurs under limited study conditions), the license application stage (where FDA reviews the results of the clinical studies and the manufacturing process), and the post-licensure stage (following approval of the product for marketing).

A sponsor seeks licensure of a complete product as it is formulated for use, not of its individual components. Human clinical studies, as required under Title 21, Code of Federal Regulations (CFR) Part 312 should provide evidence of any acute toxicity from the use of an investigational drug, including vaccines. If any ingredient or ingredients cause acute toxicity, the pre-market safety data would most likely indicate acute toxicity from use of the vaccine product. However, such data generally would not show whether any particular ingredient or combination of ingredients is the source of toxicity.

Like other approved drug and licensed biological products, vaccines licensed for marketing may also be required to undergo additional, Phase IV, studies to further evaluate the vaccine or to address specific questions about the vaccine. For example, the manufacturer of Varicella Virus Vaccine committed to perform a post-licensure study with fifteen years of safety follow-up. These studies will provide information about the effects of the vaccine in a population much larger than that exposed during clinical trials. The population will also be observed for a far longer period. If additional side effects are identified during the post-marketing phase, either pursuant to adverse event reports filed by health care providers or consumers, or pursuant to Phase IV studies, FDA would take appropriate regulatory action to protect the public health. Some of the options we would consider include changing the product's labeling information to reflect the possible side effects, or, in cases of imminent or substantial hazard to the public health, ordering a recall of the product.

Because of the complex manufacturing processes for most biological products, each product undergoes thorough laboratory testing for purity, potency, identity, and sterility. Manufacturers may release lots only after this testing is documented. FDA may require lot samples and protocols showing results of applicable tests to be submitted for review, and where appropriate, further testing by FDA. The lot release program is part of our multi-part strategy that helps ensure product safety by providing a quality control check on product specifications.

Vaccine Adverse Event Reporting System

Licensure of all vaccines marketed in the U.S. is based on a benefit-to-risk analysis of the safety and efficacy data submitted by sponsors to FDA. During the pre-market review process, manufacturers and FDA focus on identifying and understanding risks before an overall risk-benefit decision can be made on the product's licensure. When using any drug or medical product, a person runs the risk of experiencing reactions. These reactions are commonly termed "side effects." They usually are identified in clinical trials conducted before licensure and are described in a product's labeling. Known side effects, discovered in the course of clinical trials, upon which a product's licensure or approval is based, comprise the majority of reported adverse events after licensure.

Like all other medical products, vaccines are not entirely risk-free. While serious complications are rare, they can occur. Vaccines are unique medical products in that they are generally administered to a large number of healthy individuals, primarily children. Therefore, it is very important to identify even rare adverse reactions. CBER and the Centers for Disease Control and Prevention (CDC) jointly manage the Vaccine Adverse Event Reporting System (VAERS), a cooperative program for vaccine safety. VAERS is a post-marketing safety surveillance program that collects information about adverse events that occur after the administration of U.S. licensed vaccines. Any event that an individual, whether a health care provider or a consumer, believes may have resulted from the administration of a vaccine may be reported to VAERS. Such reports will be included in the system, regardless of whether there appears to be a causal relation to the vaccine. Under FDA regulations, 21 CFR, Subpart D - Reporting Adverse Experiences, section 600.80, licensed vaccine manufacturers must report to FDA adverse experience information, and establish and maintain records.

It should be emphasized that adverse event reports can be made by anyone, including health care professionals, patients, and parents. If a patient's physician does not file a VAERS report, the patient can do so. FDA protects the confidentiality of patients for whom an adverse event has been reported. FDA encourages individuals to report to VAERS any clinically significant adverse event occurring after the administration of any vaccine licensed in the U.S. Individuals who want to make a report to VAERS can call VAERS at a toll-free number, 1-800-822-7967, to obtain a reporting form. Forms and reporting instructions also are available on the Internet at www.fda.gov/cber/vaers.html and www.vaers.org. Further, VAERS reports can be made electronically at www.vaers.org.

Follow-up Study of VAERS Autism Reports

FDA has taken seriously VAERS reports of developmental delay following vaccination and wants to assure the public that the Agency is researching any possible relationship between vaccines and autism. CBER is conducting a follow-up study of VAERS reports of autism. As part of the study, CBER, in conjunction with outside autism experts, is reviewing available medical records and surveying parents and others who have reported autism after vaccinations. The goal of the interviews is to gather information about demographics, clinical features, potential risk factors, family history, vaccines administered, time interval from vaccination to autism onset, rapidity of symptom onset, and interval from diagnosis to submission of reports. Another goal is to determine how a parent makes the association between a child's autism and vaccination. Though this study will not be able to determine whether vaccines cause autism, it might suggest hypotheses that could be further evaluated in subsequent controlled, epidemiologic studies.

Autism-related Laboratory Activities

FDA is actively pursuing research involving the characterization and development of the first virus-induced animal model for autism - Borna disease virus (BDV) infection of the neonatal rat. There is no direct evidence for any relationship between BDV infection and human autism. However, BDV is used as the environmental damaging agent because it infects the brain of newborn rats. It is important to note that BDV is not a cause of autism. The damage it does and the disease syndrome it produces in rats are used only as a "model" to study general biological principles of autism. The features of this model, which FDA scientists have developed over the past ten years, have excellent correlation with what is known about human autism including neuroanatomical, behavioral, and neurochemical correlations. This model is being used in laboratories throughout the U.S. and internationally.

Thimerosal

FDA, together with other U.S. public health agencies, recognizes and supports the goal of reducing exposure to mercury from all sources. Consistent with this goal, FDA has encouraged manufacturers for several years to develop new vaccines without thimerosal as a preservative and to remove or reduce the thimerosal content of existing, licensed vaccines. This joint effort by manufacturers and FDA is reflected by the licensure of thimerosal-free products such as Comvax [Haemophilus b Conjugate Vaccine and Hepatitis B Vaccine (Recombinant) manufactured by Merck & Company, Inc.], licensed October 2, 1996, Infanrix [Diphtheria and Tetanus Toxoids and Acellular Pertussis (DTaP) manufactured by GlaxoSmithKline], licensed January 29, 1997, and Prevnar (Pneumococcal 7-valent Conjugate Vaccine manufactured by Wyeth-Lederle Vaccines and Pediatrics), licensed on February 17, 2000, and the removal or reduction of thimerosal from previously licensed products. More recently, FDA has licensed two additional thimerosal-free vaccines, Twinrix, a combination hepatitis A and B vaccine for adults (May 2001) and Daptacel, a new DTaP vaccine manufactured by Aventis Pasteur Limited (May 2002).

In response to section 413 of the Food and Drug Administration Modernization Act (FDAMA) of 1997, FDA conducted a review of the use of thimerosal in childhood vaccines. Only a relatively small number of reports mentioned thimerosal as the suspected cause of the adverse event, and our review revealed no evidence of harm caused by thimerosal used as a preservative in vaccines, except for local hypersensitivity reactions. Under the U.S. recommended childhood immunization schedule, the maximum cumulative exposure to mercury from thimerosal, at the time of this review in 1999, was within acceptable limits for the methyl mercury exposure set by FDA, the Agency for Toxic Substances and Disease Registry, and the World Health Organization. Of note, such guidelines contain safety margins and are meant as starting points for evaluation of mercury exposure, not absolute levels above which toxicity can be expected to occur. However, the maximum cumulative exposure level exceeded the more conservative limits of the Environmental Protection Agency (EPA), set to protect the developing fetus, which is believed to be more sensitive to mercury exposure. The clinical significance of exceeding EPA's limits in infants is not currently known.

Nevertheless, reducing exposure to mercury from vaccines is prudent. This is achievable, in principle, because it is possible in the U.S. to replace multi-dose vials with single dose vials, which do not require a preservative. However, there are practical and temporal issues of implementation that must be addressed.

We are pleased to be able to report substantial progress in the effort to reduce thimerosal exposure from vaccines. At this time, all routinely recommended licensed pediatric vaccines that are currently being manufactured for the U.S. market contain no thimerosal or contain only trace amounts of thimerosal. The vaccines with trace amount of thimerosal licensed to date contain less than 1 microgram of mercury per dose, that is, a given dose of vaccine contains less than 1 part per million. The use of vaccines with trace amounts of thimerosal represents a greater than 98 percent reduction from previous maximum exposure in young infants.

Our efforts over approximately the past three years to accomplish this goal include the licensure of a thimerosal-free Hepatitis B Vaccine (Recombinant) manufactured by Merck and Company in August 1999, and another hepatitis B vaccine with only a trace amount of thimerosal, manufactured by GlaxoSmithKline, in March 2000. A supplement for a new formulation of Tripedia, a DTaP vaccine manufactured by Aventis Pasteur Inc., containing only a trace amount of thimerosal was approved in March 2001. Additionally, Wyeth-Lederle Vaccines and Pediatrics now only markets a single-dose, thimerosal-free formulation of its Haemophilus b Conjugate Vaccine in the U.S.

Therefore, all routinely recommended U.S. licensed pediatric vaccines are now available in either thimerosal-free formulations or in formulations that contain only trace amounts of thimerosal. The routinely recommended vaccines include Hepatitis B Vaccine, Haemophilus b Conjugate Vaccine, Measles Mumps and Rubella Vaccine, Pneumococcal Conjugate Vaccine, DTaP Vaccine, Inactivated Polio Vaccine, and Varicella Vaccine. Prior to the recent initiative to reduce or eliminate thimerosal from childhood vaccines, the maximum cumulative exposure to mercury via routine childhood vaccinations during the first six months of life was 187.5 micrograms. With the newly formulated vaccines, the maximum cumulative exposure during the first six months of life will now be less than three micrograms of mercury. This represents a greater than 98 percent reduction in the maximum amount of mercury a child would receive from vaccines in the first six months of life.

The Immunization Safety Review Committee of the Institute of Medicine (IOM) has completed reviews in two areas relevant to today's hearing. The first review by this committee focused on a potential link between autism and the combined mumps, measles, and rubella vaccine. The IOM report provides no basis for implicating the Measles, Mumps and Rubella (MMR) vaccine as a potential cause of autism spectrum disorders (ASD). Recognizing that scientific studies can never be absolute in their conclusions, the IOM recommended further research to explore the possibility that exposure to MMR vaccine is a risk factor for ASD in a small number of children. The committee concluded that there is no need to review the existing recommendations for routine use of MMR vaccine at 12-15 months of age and 4-6 years of age. The Committee's conclusion supports the current policy of giving the MMR vaccine as a combination vaccine instead of administering each of the components (measles, mumps and rubella) separately. The second review focused on a potential relationship between thimerosal use in vaccines and neurodevelopmental disorders (IOM 2001). In its report of October 1, 2001, the IOM's Immunization Safety Review Committee concluded that the evidence is inadequate to either accept or reject a causal relationship between thimerosal exposure from childhood vaccines and the neurodevelopmental disorders of autism, attention deficit hyperactivity disorder (ADHD), and speech or language delay. Thus, while the available scientific data do not establish that these neurodevelopmental disorders are caused by thimerosal, at the same time, they do not establish that these neurodevelopmental disorders are not caused by thimerosal. Additional studies are needed to establish or reject a causal relationship. The Committee did conclude that the hypothesis that exposure to thimerosal-containing vaccines could be associated with neurodevelopmental disorders was biologically plausible.

The Committee believed that the effort to remove thimerosal from vaccines was "a prudent measure in support of the public health goal to reduce mercury exposure of infants and children as much as possible." Furthermore, the Committee urged that "full consideration be given to removing thimerosal from any biological product to which infants, children, and pregnant women are exposed."

The FDA is continuing its efforts to reduce the exposure of infants, children, and pregnant women to mercury from all sources. Discussions with the manufacturers of influenza virus vaccines (which are routinely recommended for pregnant women) regarding thimerosal-reduced and thimerosal-free presentations are ongoing. Two of the three influenza virus vaccines, Fluvirin from Evans Vaccines and Fluzone from Aventis Pasteur, Inc., are now available in a formulation that contains only trace thimerosal. The third manufacturer of influenza virus vaccine, Wyeth Laboratories, has announced that starting next year it will no longer manufacture flu vaccine. Discussions are also underway with regard to other vaccines, in particular, the diphtheria and tetanus vaccines and one manufacturer's adolescent/adult formulation of the hepatitis B vaccine (a second manufacturer's hepatitis B vaccine contains only trace thimerosal for both the pediatric and adult formulations.) In addition, all immune globulin preparations including hepatitis B immune globulin and Rho(D) immune globulin preparations are now manufactured without thimerosal.

Thimerosal and the National Toxicology Program

The National Toxicology Program (NTP) was established in 1978 by the Secretary of the Department of Health and Human Services (DHHS or the Department) to coordinate toxicology research and testing activities within the Department, to provide information about potentially toxic chemicals to regulatory and research agencies and the public, and to strengthen the science base in toxicology. The NTP has become a world leader in designing, conducting, and interpreting animal assays for toxicity and/or carcinogenicity.

NTP uses a chemical nomination and selection process as a means to best use its resources with respect to the testing of chemicals of greatest health concern. Member agencies of the NTP, including FDA, are the primary sources of nominations to the NTP. Because of the continued interest on the part of the public, as well as public health agencies, to better characterize the potential toxicity that could have accompanied an exposure to thimerosal from vaccines, FDA has nominated thimerosal to the NTP for further study to adequately assess gaps in knowledge regarding, among other things, neurodevelopmental toxicity. The nomination was accepted by the review committee earlier this year.

Vaccine Recall

Federal law is specific about the criteria that must be met before FDA can order a mandatory recall of a regulated product. Under section 351(d) of the Public Health Service Act, a licensed vaccine (or other biological product) shall be recalled if FDA determines that it ". . . presents an imminent or substantial hazard to the public health . . ." The available scientific data do not provide conclusive evidence that exposure to thimerosal in vaccines can cause neurodevelopmental disorders. Therefore, FDA does not have the scientific basis to conclude that thimerosal-containing vaccines "present an imminent or substantial hazard to the public health" for a recall order.

FDA regulations also provide for a voluntary recall of products regulated by the FDA (21 CFR, Part 7). A firm may withdraw a product from the market, of its own volition, at any time. In addition, FDA may request a firm to recall a product that is in violation of FDA laws and regulations and that presents a risk of injury or gross deception, or is otherwise defective. An agency request for recall is reserved for urgent situations such as those that are necessary to protect the public health. FDA has concluded that the scientific data and other information do not support an FDA request for a voluntary recall. Vaccines are not violative per se because they contain thimerosal as a preservative and there is no conclusive data that they present a risk of injury. Additional studies on the potential for adverse effects of mercury in vaccines are continuing. Results of these studies will be closely monitored by FDA.

That concludes my testimony. I would be happy to respond to any questions.

Mr. BURTON. Dr. Foote.

Mr. FOOTE. Mr. Chairman, members of the committee, I am Dr. Steve Foote, Director of the Division of Neuroscience and Basic Behavioral Science of the National Institute of Mental Health. I am accompanied by Dr. Christopher Portier, Director of the Environmental Toxicology Program at the National Institute of Environmental Health Sciences.

I am the witness representing the National Institutes of Health today because I play several roles in the coordination, planning, and oversight of autism research at NIH. For example, I serve as a scientific program staff member of the NIH Internal Autism Coordinating Committee, a longstanding body that serves to coordinate autism research NIH-wide. Also, I have played a major role in organizing and implementing the NIH centers program called for in the Children's Health Act of 2000, which we have named the Studies to Advance Autism Research and Treatment, or STAART, Centers Program. Finally, I have served a leadership role in the establishment and operation of the Department of Health and Human Services' Interagency Autism Coordinating Committee that was created under a provision of the Children's Health Act of 2000.

I appreciate the opportunity to talk with you about NIH's support of research on autism. I am a neuroscientist who has been interested in the brain and its disorders throughout my career, and, like others, I have found autism to be a particularly challenging mystery.

My view of this disorder has been broadened and deepened by my continuing interactions with members of the families with autistic children and adults. I feel their urgency. An affected child cannot wait for research before growing up. Any potential improvement is crucial.

I would like to acknowledge the important role of families and advocacy groups in our efforts. They have not only raised the visibility of autism and challenged assumptions; they have pushed for and often funded I might say, accelerated and expanded research activities.

I testified before this committee earlier this year, but now there is even more recent progress to report. The basic research on autism that is sorely needed is moving forward at an ever-accelerating pace, as is continued genetic research and studies of the etiology of various autism spectrum symptoms, including communication disorders and interpersonal difficulties. Autism biomedical research is rapidly expanding as the scope and level of detail of scientific topics under active investigation is aggressively broadened.

Several weeks ago, I attended the Second Annual International Meeting for Autism Research. This meeting was an exciting forum for this rapidly growing field. It was a meeting that just could not have even been imagined just a few years ago in terms of its scope and quality.

Extremely important funding programs from voluntary organizations and other Federal agencies, along with very substantial increases in NIH funding that have occurred over the past several years, have provided financial support underlying this growth in volume and quality of research. Other driving forces have been the advances of closely related biomedical research fields such as genomics and neuroscience that have provided the necessary knowledge and tools for more powerful and promising insights into the biological nature of autism.

In summary, biomedical research into autism is advancing rapidly and NIH is playing a major role in this progress.

I am also pleased to report that as part of the enhanced activities in this area, NIH has made much progress in implementing the provisions of the Children's Health Act of 2000 that focused on NIH research activities related to autism. In terms of the requirement for a new centers of excellence program, NIH has issued a total of three requests for applications, RFAs, to implement on a fast track, the STAART Centers program. An RFA, as you know, is a clear statement to the scientific field, setting aside funds that NIH invites research in a particular area. The first RFA was for developmental grants. Those were reviewed. We funded six of those. The second RFA was for an initial round of competition for full center support. A number of applications were received, reviewed in March 2002, and two centers were funded. A second round of competition for full center support is in mid-cycle and the applications are being reviewed yesterday and today. And I was at those reviews all day yesterday and I was able to attend most of the reviews today, and they are going very well.

When these successful applications from this round of competition are funded during fiscal year 2003, the full network of at least five centers stipulated by the law will be in place. The five participating NIH Institutes—NIMH, the National Institute of Neurological Disorders and Stroke, the National Institute of Child Health and Human Development, the National Institute on Deafness and Other Communication Disorders, and the National Institute of Environmental Health Sciences—have committed up to $12 million a year, including $8 million from NIH, to fund this network at that level for over 5 years—for up to 5 years. This is a commitment of $60 million minimum.

Another component of the Children's Health Act was the establishment of an Interagency Autism Coordinating Committee, the IA CC as we call it. The Secretary of the Department of Health and Human Services delegated to NIH the authority to organize the IACC, and NIMH was asked to lead this effort. The IACC has been organized and has now had its first three semiannual meetings. It is actively pursuing its mandate to enhance communication and effective interaction among the several agencies that support or conduct autism-related research, service, or educational activities, and it has engaged family and advocacy groups largely through the public members that were appointed by the Secretary.

In addition to these activities, NICHD and NIDCD have competitively renewed their longstanding collaborative programs of excellence in autism. The NIH is fully committed to this important program, and will continue its support for both CPEA and STAART programs for several years into the future. And yet another recent enhancement of the NIH autism research portfolio, NIEHS, has funded two centers focused on autism research.

We at the NIH are at a heightened state of awareness concerning the need for more research on autism due to the clear magnitude of this major public health problem and due to the work of many people within and outside this room. We have been making progress. In fiscal year 1998, NIH support for autism research totaled about $26 million; by fiscal year 2001, which is the latest year for which we have official numbers, the total was about $55 million.

To put this in perspective, the NIH commitment to autism research has more than doubled in these few years.

In terms of the specific questions in your letter of invitation, there are a number of active and planned projects that address the concerns you raise. NIH recently furnished you with a summary of the research activities sponsored by the National Institute of Allergy and Infectious Diseases and by NIEHS designed to address questions about thimerosal, ethyl and methyl mercury, and the search for other environmental risk factors for autism.

Another question you raised was about treatments, and several institutes are sponsoring numerous projects dealing with treatment interventions for autism, and the STAART Centers Program includes a primary emphasis on such studies.

So to summarize and finish, NIH is on schedule in terms of implementing the letter and the spirit of all aspects of Title I of the Children's Health Act, including a broadly based increase in autism research support, the initiation of a new centers of excellence program, and enhancement of genetic and other research resources, and the establishment of the Interagency Autism Coordinating Committee.

That concludes my testimony. And Dr. Portier and I would be glad to answer any questions.

[The prepared statement of Mr. Foote follows:]

Testimony
Before the Committee on Government Reform
United States House of Representatives

"Vaccines and the Autism Epidemic"

Statement of

Stephen L. Foote, Ph.D.

Director,
Division of Neuroscience and Basic Behavioral Science,
National Institute of Mental Health,
National Institutes of Health,
U.S. Department of Health and Human Services

For Release on Delivery
Expected at 1:30pm
on Tuesday, December 10, 2002

Mr. Chairman, Members of the Committee. I am Dr. Steve Foote, Director of the Division of Neuroscience and Basic Behavioral Science at the National Institute of Mental Health. I am the witness representing the National Institutes of Health (NIH) today because I play several roles in the coordination, planning, and oversight of autism research at NIH. For example, I serve as a scientific program staff member of the NIH internal Autism Coordinating Committee (NIH/ACC), a long-standing body that serves to coordinate autism research NIH-wide. Also I have played a major role in organizing and implementing the NIH centers program called for in the Children's Health Act of 2000 (P.L. 106-310), which we have named the Studies to Advance Autism Research and Treatment (STAART) Centers program. Finally, I have served a leadership role in the establishment and operation of the Department of Health and Human Services (HHS), Interagency Autism Coordinating Committee (IACC) that was created under a provision of the Children's Health Act of 2000.

I appreciate the opportunity to talk with you about NIH support of research on autism. I am a neuroscientist who has been interested in the brain and its disorders throughout my career, and, like others, I have found autism to be a particularly challenging mystery. My view of this disorder has been broadened and deepened by my continuing interactions with members of families with autistic children and adults. I feel their urgency: an affected child cannot wait for research before growing up. Each day, each potential improvement, is crucial. I would like to acknowledge the important role of families and advocacy groups in our efforts. They have not only raised the visibility of autism and challenged assumptions, they have pushed for accelerated and expanded research activities.

I testified before this Committee earlier this year, but now there is even more recent progress to report. The basic research on autism that is sorely needed is moving forward at an ever accelerating pace, as is continued genetic research, and studies of the etiology of various autism spectrum symptoms including communication disorders and interpersonal difficulties. Autism biomedical research is rapidly expanding as the scope and level of detail of scientific topics under active investigation is aggressively broadened. Several weeks ago I attended the Second Annual International Meeting For Autism Research. This meeting was an exciting forum for this rapidly growing field. Extremely important funding programs from voluntary organizations and other federal agencies, along with very substantial increases in NIH funding of this area that have occurred over the past several years, have provided the financial support underlying this growth in volume and quality of research. Other driving forces have been the advances of closely related biomedical research fields, such as genomics and neuroscience that have provided the necessary knowledge and tools for more powerful and promising insights into the biological nature of autism. In summary, biomedical research into autism is advancing rapidly, and NIH is playing a major role in this progress.

I am also pleased to report that as part of the enhanced activities in this area NIH has made much progress in implementing the provisions of the Children's Health Act of 2000 that focused on NIH research activities related to autism. In terms of the requirement for a new centers of excellence program, NIH has issued a total of three Requests For Applications (RFA) to implement, on a fast-track, the STAART Centers program. An RFA is a clear statement to the field – setting aside funds – that NIH invites research in a particular area. The first RFA was for developmental grants to provide funds for teams of investigators as they prepared to compete for full center support. Six grants were awarded under this RFA. The second RFA was for an initial round of competition for full center support. A number of applications were received, reviewed in March 2002, and two centers were funded. A second round of competition for full center support is in mid-cycle, and the applications are being reviewed yesterday and today. When the successful applications from this round of competition are funded next year, the full network of at least 5 centers stipulated by the law will be in place. The 5 participating NIH institutes [NIMH, the National Institute of Neurological Disorders and Stroke (NINDS), the National Institute of Child Health and Human Development (NICHD), the National Insitute on Deafness and Other Communication Disorders (NIDCD), and the National Insitute of Environmental Health Sciences (NIEHS)] have established a pool of $12M per year (including $8M per year from NIMH) to fund this network. This is $60 million at a minimum.

Another component of the Children's Health Act was the establishment of an Interagency Autism Coordinating Committee - the IACC. The Secretary of the Department of Health and Human Services delegated to NIH the authority to organize the IACC, and NIMH was asked to lead this effort. The IACC has been organized and has now had three semi-annual meetings. It is actively engaged in its mandate to enhance communication and effective interaction among the several agencies that support or conduct autism-related research, service, or educational activities, and it has engaged family and advocacy groups, largely through the public members that were appointed by the Secretary. The NIH/ACC provides a continuing framework that allows program scientists and directors of the relevant institutes to come together to plan and conduct research, and it communicates closely with the IACC.

In addition to these activities, NICHD and NIDCD have competitively renewed their long-standing Collaborative Programs of Excellence in Autism (CPEA). The NIH is fully committed to this important program, and will continue its support for both CPEA and STAART programs for several years into the future. In yet another recent enhancement of the NIH autism research portfolio, NIEHS has funded two centers focused on autism research.

We at the NIH are at a heightened state of awareness concerning the need for more research on autism: due to the clear magnitude of this major public health problem and due to the work of many people within and outside this room. And, we have been making progress. In FY 1998, NIH support for autism research totaled about $26M: by FY 2001, the total was about $55M. To put this in perspective, the NIH commitment to autism research more than doubled in these few years. In terms of the specific questions in your letter of invitation, there are a number of active and planned projects that address the concerns you raise. NIH recently furnished you with a summary of the research activities sponsored by the National Institute of Allergy and Infectious Diseases and NIEHS designed to address questions about thimerosal, ethyl and methyl mercury, and the search for other environmental risk factors for autism. Several institutes are sponsoring numerous projects dealing with treatment interventions for autism, and the STAART Centers program will include a primary emphasis on such studies.

In summary, NIH is on schedule in terms of implementing the letter and the spirit of all the aspects of Title I of the Children's Health Act, including a broadly based increase in autism research support, the initiation of a new centers of excellence program, an enhancement of genetic and other research resources, and the establishment of the IACC.

That concludes my testimony. I would be happy to answer any questions.

Mr. BURTON. Thank you. I just have a few questions here, and then I'm going to let Dr. Weldon ask some questions. But I will have a number of other ones that I think are relevant and important after he concludes.

I believe Dr. Geier indicated that since the 1980's, there have been 1,500-plus articles written in scientific journals about the problems with mercury and thimerosal. Why haven't the health agencies of our government done something about it before now; 1,500 articles. Dr. Midthun.

Dr. MIDTHUN. The review that we did in response to FDAMA went over the literature that existed, and it was our assessment that certainly, as Dr. Baskin was saying, we all know that mercury itself in larger amounts is clearly a toxicant. But our assessment was that the amounts that were present in the vaccines, that there did not—there was—that those were safe and effective, and that certainly though our assessment was that whenever possible it's good as a precautionary measure to limit the exposure to mercury from any sources, and in the United States, since we do have the ability and principal to use to single-dose presentations that don't require a preservative, that would be the appropriate precautionary step to take.

Mr. BURTON. Why haven't we done that before now? I mean, in 1998, the FDA showed it was concerned about the neurotoxic effect of mercury from cumulative dosing. And if you look at exhibit No. 3—do you have that in front of you?

[Exhibit 3 follows:]

MEMORANDUM

Date: September 17, 1998

From: Marion F. Gruber, Ph.D, DVRPA/OVRR

To: M.C. Hardegree, M.D., Director, OVRR
N. Baylor, Ph. D.

Through: K. Goldenthal, M.D., Director, DVRPA

Subject: POINT PAPER "PRECLINICAL REPRODUCTIVE TOXICITY STUDIES FOR VACCINES"

Purpose:

a) To obtain feedback and concurrence from OVRR and CBER upper management on the recommendations made by the maternal immunization working group with regard to reproductive toxicity study requirements for vaccines pending licensure and to obtain concurrence that these recommendations may be used in discussing reproductive toxicity study requirements with sponsors

b) To generate a working document to promote consistency among OVRR reviewers

This document does not contain detailed proposals for reproductive toxicity studies for specific vaccine products. These will be the subjects of further discussions by the maternal immunization working group provided that concurrence on the concepts contained in this document have been obtained.

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Rationale: Maternal immunization is intended to prevent infectious disease in the vaccinee and/or young infant through passive antibody transfer from mother to fetus. Although preclinical reproductive toxicity studies prior to licensure of vaccines intended for maternal immunization and/or women of child bearing age are critical in assessing the potential for the developmental toxicity of the product, OVRR has no written policy to date addressing such requirements. In addition, the performance and design of preclinical reproductive toxicity studies for vaccines to support their use for maternal immunization has not been addressed in the scientific literature. A maternal immunization working group was formed in January of 1998 which includes scientific staff from OVRR and toxicologists from OTRR and CDER[1].

The purpose of this working group is to optimize the advice given to sponsors regarding the preclinical testing for specific

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[1] Previous attendees of the maternal immunization working group: *CBER/OVRR:* M.Gruber, M.Hardegree, N.Baylor, K.Goldenthal, D.Chandler, K.Midthun, D.Pratt, V.Johnson, J.Clifford, L.Ball, A.Geber, C.Frasch, C.Deal, L.McVittie, L.Henchal, L.Falk, M.Monser, P.Richman, B.Sheets; *CBER/OTRR:* D.Green, M.Serabian, CDER:K.Hastings

EXHIBIT

vaccine products as well as to develop comprehensive policy for reproductive toxicity study requirements for vaccines indicated for maternal immunization and/or immunization of women of childbearing age.

The following summarizes the recommendations for reproductive toxicity studies for vaccines:

Preclinical Reproductive toxicity studies for vaccines indicated for immunization of pregnant women:

Reproductive toxicity studies should be conducted for every vaccine indicated for immunization of pregnant women. These studies should be completed prior to initiation of Phase 1 clinical trials involving pregnant women.

In addition to safety trials in pregnant women pre-licensure, pregnancy registries should be established for the purpose of effectively monitoring for any adverse events experienced by the vaccinated pregnant females, as well as to track any developmental toxicities displayed by the offspring post licensure.

Preclinical reproductive toxicity studies for vaccines indicated for immunization of adolescents and adults

Reproductive toxicity studies should be conducted prior to licensure for all vaccines indicated for adolescents and adults of childbearing age due to the increasing number of vaccines that are recommended for this population even though this has not been required by OVRR in the past. This position is further supported by the fact that reproductive toxicology studies are required for some products licensed by OTRR and for the majority of products that are regulated by CDER. Further discussions will be needed regarding the stage of product development by which the preclinical reproductive toxicity evaluation should be completed.

It is recommended that pregnancy registries be established to monitor the safety of these vaccines post licensure. Of particular concern is the administration of the vaccine to pregnant individuals.

[Note that in CDER data from teratogenicity studies are generally obtained before proceeding to Phase 2 studies. All reproductive toxicity studies, to include male fertility, teratogenicity, and postnatal development, are generally conducted before initiating Phase 3 clinical trials.]

Preclinical versus clinical experience with vaccines:

Clinical data that may have been obtained from a small number of pregnant women enrolled in non-IND studies immunized with an investigational vaccine do not replace the need for comprehensive reproductive toxicity studies.

However, clinical experience derived from immunization of pregnant women may be helpful in the evaluation of the potential for any adverse outcome on the viability and development of offspring. Such information may also aid in the design/monitoring of appropriate preclinical studies.

Design of reproductive toxicity studies

Males

The potential adverse effects on male fertility should be assessed if the vaccine indication includes the male population. This is particularly important for products that are given to military forces, e.g., the Anthrax and Botulinum toxoid vaccine. However, additional discussion will be required regarding the details of the types of studies needed for these products. The ICH S5B document may serve as guidance in the design of these studies (Reproductive Toxicology: Male fertility studies, April 5, 1996, FR 15360, Vol.61, No. 67)

Females

While the type of study performed depends on the clinical indication and the product, in general, relevant information can be obtained by conducting Segment II teratology studies and/or studies designed following stages C - E of the ICH guidance document entitled "Detection of Toxicity to Reproduction for Medicinal Products" (September 22, 1994, FR 48746, Vol.59, No. 183)

It is important that a postpartum follow-up period be included in the design of the study, in order to evaluate the active immune response in the offspring following vaccination of pregnant females.

The reproductive toxicity study should be designed to include:
1) the detection of antibody production in the pregnant animal;
2) the feasibility of antibody transfer from the pregnant female to the fetus through antibody measurements in the newborn.

General Considerations

All available clinical experiences in pregnant females should be considered for any potential application to the design of reproductive toxicity studies in animals.

All data generated from prior acute or repeat dose preclinical toxicity studies should be reviewed for their possible contribution to the interpretation of any adverse developmental effects that appear in the reproductive toxicology studies.

Reproductive toxicity studies should include a dose response component in order to assess 1) the ability of a certain dose of vaccine to elicit an antibody response and 2) the effect(s) that a particular dose has on the dam and on the conceptus.

The immunization interval and frequency of immunization(s) in a reproductive toxicity should be based on the clinically proposed immunization interval and its timing, i.e., use of the vaccine at pre-conception or during the 1st, 2nd, and/or 3rd trimester.

Reproductive toxicity studies for vaccines similar in structure and/or activity to other compounds:

Although the reproductive toxicity potential of a "prototype" vaccine may have been assessed and the similarity between the "prototype" vaccine and a new investigational vaccine(s) may have been established in terms of the manufacturing process, product characterization and clinical safety, additional reproductive toxicity studies using the final clinical vaccine formulation may be necessary (e.g., 9 versus 11-valent pneumococcal conjugate vaccine; multivalent versus monovalent GBS vaccine). [Note that in CDER, reproductive toxicology studies are usually performed for every new "molecular entity", with only few exceptions.]

Reproductive toxicity studies should be performed for all vaccines that belong to a similar class (e.g., polysaccharide vaccines), but which contain components derived from different organisms, or where different manufacture and/or purification procedures are employed.

Use of mercury containing preservatives in vaccines intended for maternal immunization:

The FDA Modernization Act (FDAMA) of 1997, Section 413 (c)(2), states that "...regulations shall be designed to protect the health of children and other sensitive populations from adverse effects resulting from exposure to, or ingestion or inhalation or mercury."

For investigational vaccines indicated for maternal immunization, the use of single dose vials should be required to avoid the need of preservative in multi dose vials as required by the Code of Federal Regulations (CFR). Of concern here is the potential neurotoxic effect of mercury especially when considering cumulative doses of this component early in infancy. All mercury-containing vaccine formulations should be evaluated in appropriate preclinical reproductive toxicology studies that include the assessment of postnatal behavioral and developmental endpoints (This topic is being addressed by the FDA-wide working group on mercury-containing drugs).

CBER/DVRPA:preparedbyMGruber(DVRPA):8/17/98

Pregnancy Registry Initiatives

Presentation to the CBER
Maternal Immunization Working Group
October 13, 1998

Heidi M. Jolson, M.D., M.P.H.

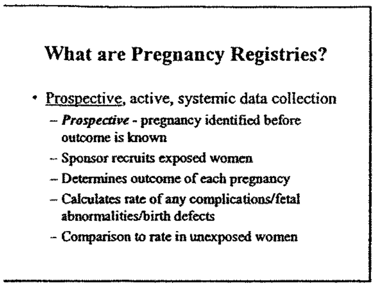
Current Situation

- New drugs infrequently studied in pregnant women
  - Lack of human information in the label
- Extrapolation of preclinical study results to humans often uncertain
- Many problems with pregnancy category system in label
- Lack of sponsor incentives to develop information

Pregnancy Labeling Taskforce:

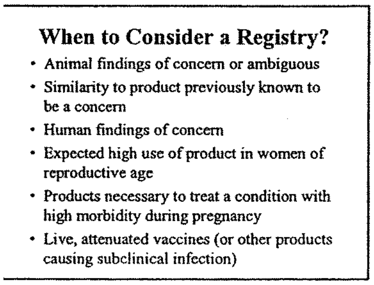
An Agency-wide initiative

Preclinical Working Group	Clinical Working Group
• Reviewer guidance document on reproductive and developmental toxicology data	• *Reviewer guidance document on human pregnancy outcome data* • *Industry guidance document on registries* • *Reviewer training*



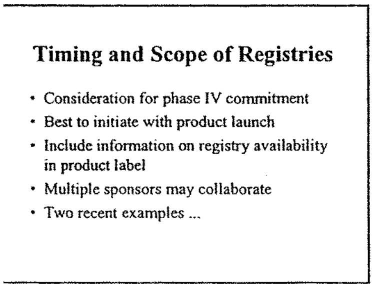
What are Pregnancy Registries?

- Prospective, active, systemic data collection
  - *Prospective* - pregnancy identified before outcome is known
  - Sponsor recruits exposed women
  - Determines outcome of each pregnancy
  - Calculates rate of any complications/fetal abnormalities/birth defects
  - Comparison to rate in unexposed women



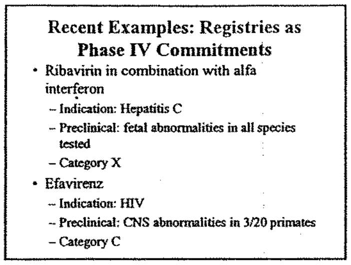
When to Consider a Registry?

- Animal findings of concern or ambiguous
- Similarity to product previously known to be a concern
- Human findings of concern
- Expected high use of product in women of reproductive age
- Products necessary to treat a condition with high morbidity during pregnancy
- Live, attenuated vaccines (or other products causing subclinical infection)



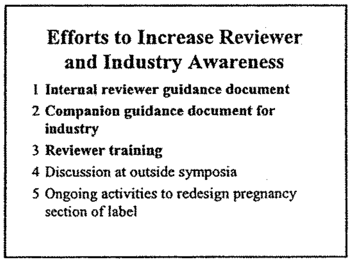
Timing and Scope of Registries

- Consideration for phase IV commitment
- Best to initiate with product launch
- Include information on registry availability in product label
- Multiple sponsors may collaborate
- Two recent examples ...



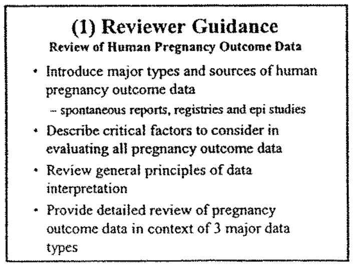
Recent Examples: Registries as Phase IV Commitments

- Ribavirin in combination with alfa interferon
  - Indication: Hepatitis C
  - Preclinical: fetal abnormalities in all species tested
  - Category X
- Efavirenz
  - Indication: HIV
  - Preclinical: CNS abnormalities in 3/20 primates
  - Category C



Efforts to Increase Reviewer and Industry Awareness

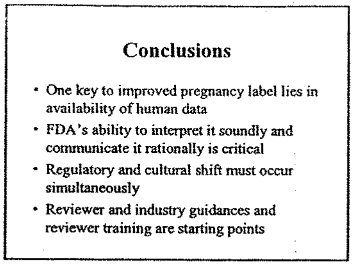
1 **Internal reviewer guidance document**
2 **Companion guidance document for industry**
3 **Reviewer training**
4 Discussion at outside symposia
5 Ongoing activities to redesign pregnancy section of label



(1) Reviewer Guidance

Review of Human Pregnancy Outcome Data

- Introduce major types and sources of human pregnancy outcome data
  - spontaneous reports, registries and epi studies
- Describe critical factors to consider in evaluating all pregnancy outcome data
- Review general principles of data interpretation
- Provide detailed review of pregnancy outcome data in context of 3 major data types



Conclusions

- One key to improved pregnancy label lies in availability of human data
- FDA's ability to interpret it soundly and communicate it rationally is critical
- Regulatory and cultural shift must occur simultaneously
- Reviewer and industry guidances and reviewer training are starting points

Criteri	Ranking
A. Participant enrollment • Was all enrollment prospective? • Were women actively recruited or did they initiate contact? • When was the exposure to the target drug ?	
B. Data collected at enrollment • Timing of enrollment from exposure, from identification of pregnancy? • Did they accurately assess the drug, dose, timing and extent of exposure? • What additional information was collected: indication, medical history, past pregnancies and their outcomes, socio-demographics, smoking, alcohol consumption, etc.?	
C. Data collected during follow-up • What was the method and extent of follow-up? How frequent were the contacts? • Was drug exposures and other information properly ascertained at each contact? • Did they minimize losses to follow-up? Could differential follow-up bias the results?	
D. Determination of pregnancy outcome • How and when were major anomalies ascertained for births, abortions? • How and when were minor anomalies ascertained? • How were additional and secondary outcomes defined and ascertained? • Were physical or pathological examinations conducted? How and by whom?	
E. Analysis and Interpretation • Was the risk of each outcome properly calculated with confidence intervals? • Was the minimal detectable risk (properly) estimated? • Was variation in risk assessed? Are groupings and analyses appropriate? • How do the results change if all lost had adverse outcome? None had adverse outcome? Are study results valid in light of the proportion lost to follow-up? • Does the medical condition elevate the risk of the adverse outcome? Could the drug further elevate that risk? • Relative risk - Was the comparison group appropriate? Did they compare anomaly rates among women with the same medical condition, pregnancy history, socio-demographics?	

C:\AAA\PREG\REGIST3.DOC

Gruber, Marion

From: Ken Hastings 301-827-2336 FAX 301-827-2523 [HASTINGSK@cder.fda.gov]
ent: Wednesday, October 14, 1998 3:23 PM
o: M CAROLYN HARDEGREE (FDACB)
: KAREN L GOLDENTHAL (FDACB); MARION F GRUBER (FDACB); Frank Sistare; Steve Hundley
Subject: Thimerosal

Sensitivity: Confidential

Carolyn: Steve Hundley, a Pharm/Tox reviewer in DSPIDP, has just about completed a review I asked him to do of the published Pharm/Tox information on thimerosal. I will forward his review to you when it is finalized, but his conclusion, basically, is that there is little in the literature to support the idea that thimerosal is a significant hazard at the doses used in vaccine products, but that there might be some "holes" in the data base that could be addressed by appropriate animal studies (e.g. repro tox, metabolism). I have had some communication with Frank Sistare, Director of Applied Pharm Research in OTR, concerning possibly doing some tox studies with thimerosal, but one issue that Frank would like some clarification on is the importance of the issue. My response was that this was probably going to be fairly important, based on the need to use thimerosal in multi-use vials, and the fact that the Europeans appear to want to essentially ban it from use in vaccines and that (I thought) there was some language in FDAMA about removing mercury-containing preservatives from drugs and biologics. I think Frank wants to get a sense of the scope of this issue before getting too involved in looking at research possibilities. Can you give us some idea as to how serious this issue is?

Thanx-
Ken

Maternal Immunization working group
10/13/98

✓

List of attendees

Marion Gruber	OVRR /DVRPA
Carolyn Hardegree	OVRR
Mercedes Serabian	OTRR / DCTDA
Norman Baylor	OVRR
Becky Sheets	DVRPA
Heidi Jolson	CDER/DAVDP
Karen Midthun	OVRR/ DVRPA
Ken Hastings	CDER/DSPIDP
Julianne Clifford	CBER/DVRPA
LYDIA FALK	CBER/DVRPA
[illegible]	CBER/DVRPA

Dr. MIDTHUN. No, I don't. Could I please see those?

Mr. BURTON. Give that to them, would you please.

I want to read you what—this is a memo from Dr. Marianne Gruber to Dr. Carolyn Hardegree and Dr. Norman Baylor of the FDA. It's dated September 17, 1998, and it's entitled "Point Paper, Preclinical Reproductive Toxicity Studies for Vaccines."

And on No. C there, if you are looking at it, it says—Dr. Gruber says, for investigational vaccines indicated for material immunization, the use of single-dose files should be required to avoid the need of preservatives in multi-dose vials as are required by the Code of Federal Regulations. Of concern here is the potential neurotoxic effect of mercury, especially when considering cumulative doses of this component early in infancy. All mercury-containing vaccine formulations should be evaluated in appropriate preclinical reproductive toxicology studies that include the assessment of postnatal, behavioral, and developmental end points.

Read that?

Dr. MIDTHUN. I am sorry, I don't see point C on here. I am looking at exhibit 3, and I see A and B.

Mr. BURTON. It's on page 4.

Dr. MIDTHUN. Page 2—3.

Mr. BURTON. And these are some of your——

Dr. MIDTHUN. I still—I'm sorry, don't see point C on page 4. I see the heading, the first bold heading.

Mr. BURTON. The last paragraph down at the bottom.

Dr. MIDTHUN. For investigational vaccines indicated for maternal immunization. That paragraph?

Mr. BURTON. Yeah.

Dr. MIDTHUN. OK. Let me take a look at that, please.

Mr. BURTON. All right.

Dr. MIDTHUN. This is a specific reference to maternal immunizations, specifically evaluating investigational vaccines to administer to pregnant women.

Mr. BURTON. Right.

Dr. MIDTHUN. And there, you know, the—obviously, again, as a precautionary measure to limit the exposure to mercury and also to evaluate any vaccine that is investigational that you are trying to evaluate for that particular use that these kinds of studies should be done. So this is a specific reference to vaccination of pregnant women, for vaccines indicated for them.

Mr. BURTON. So let me get this straight. There are 1,500 articles written about the problems with thimerosal and vaccines, we have had a 40fold increase in the number of children that are autistic, You had this statement regarding pregnant women, and yet you didn't think that there was any concern about children, infants, getting these vaccines that had thimerosal in them at that time?

Dr. MIDTHUN. Again, I haven't had an opportunity to look at this whole—this whole memorandum, but I think that clearly this relates to a time pursuant to the FDAMA—FDA Modernization Act of 1997—when a process was initiated to review mercury in general in all drugs and biologics, including, of course, vaccines.

Mr. BURTON. Do you think mercury is a bad thing to be putting in your body?

Dr. MIDTHUN. I think we recognize that mercury in large amounts clearly is harmful.

Mr. BURTON. How much is a large amount?

Dr. MIDTHUN. You know, there are different studies that have been done to look at that. And I think that some of the studies that came out of the Faroe Islands indicated that perhaps lower amounts could cause problems based on subtle year developmental observations that were seen in that study. Although my understanding was that some of the interpretations of that study were also somewhat confounded by the probable exposure to PCBs.

Mr. BURTON. Enough. Enough. That's enough. I just don't want to hear any more of that. Take a look at this slide that's up here, would you please. That shows the amount of money that is spent on diabetes at the top, AIDS next, and autism at the bottom. And autism is one of the fastest growing epidemics in the country. Why is it we're spending such a small amount on research? I know Dr. Foote says we're spending more. But even if we were spending the $55 million you're talking about we're spending $2,770,000 on AIDS and $845,000 on diabetes, not to diminish those, they're very important.

But one of the fastest growing, if not the fastest growing epidemic in the country is autism. And we're spending just a minute amount on that when we're going to have these kids with us for life and they're damaged. Why is it more research hasn't been done before now?

Mr. FOOTE. Well, as you know, these budget figures are the bottom line of a very complex set of processes. Certainly we are doing—we are engaged in a lot of activities designed to increase the number of investigators who are capable of constructively utilizing research funding to study questions about autism. And that's one of the major hopes we have for the autism centers program is that these will create sites at which young people can get intensive training in autism-related issues. And it is our full expectation that then they will become qualified and highly competitive investigators for NIH funds.

Mr. BURTON. How many studies are currently going on?

Mr. FOOTE. How many autism-related research grants——

Mr. BURTON. Studies, that the Federal Government is funding, how many are going on right now that are started?

Mr. FOOTE. I don't think I can speak for the entire Federal Government, but there are five NIH institutes that fund autism research and it runs up into probably a few hundred grants.

Mr. BURTON. When does all this start, do you know?

Mr. FOOTE. Well, as I indicated in my opening remarks, autism research has been going on in some substantial degree for at least a decade at NIH, but the exponential curves that we've been discussing certainly apply to the amount of money going into autism research, which has increased very dramatically over the past few years.

Mr. BURTON. Are there still vaccines in doctors' offices right now today that contain thimerosal that are being given to children?

Dr. MIDTHUN. I don't believe so, no. As I mentioned, all vaccines for the routine recommended childhood immunization series started 2001 have been manufactured either thimerosal free or with markedly reduced amounts of that thimerosal. Now, that's just the vaccines that are in the routinely recommended immunization schedule. As I mentioned, influenza vaccines which are not part of that recommended schedule but were encouraged to be administered by the ACIP, although they're not yet part of the routine schedule, those are now available in a thimerosal trace formulation for both of Evans vaccines and Aventis Pasteur vaccines.

As I mentioned, Wyeth announced its intentions not to manufacture an influenza vaccine after this year. But the other two do offer this trace thimerosal presentation. However——

Mr. BURTON. But they still have that thimerosal in them.

Dr. MIDTHUN. Yes, they still also have multi-dose vials that do contain——

Mr. BURTON. Why don't they go to single-dose vials?

Dr. MIDTHUN. I know that they are considering the feasibility of——

Mr. BURTON. Why don't you tell them to do that?

Dr. MIDTHUN. We consider these vaccines, which also contain thimerosal as a preservative to be safe and effective. However, we do consider that it's important to have vaccines——

Mr. BURTON. Did you hear any of the testimony earlier from those people that were testifying, those scientists and doctors?

Dr. MIDTHUN. Yes, I did.

Mr. BURTON. Did you see the study from Canada there that showed the damage that's done when a very minute amount of mercury is given, put in proximity to brain cells.

Dr. MIDTHUN. I think it's hard to extrapolate that data to what actually happens in a clinical situation.

Mr. BURTON. You know, every study that's been done, Doctor, that you guys put forth showing that there's no correlation between thimerosal and autism doesn't say categorically that thimerosal doesn't cause autism. They never say that. Can you are tell me right now categorically without any doubt whatsoever that mercury in vaccines does not cause autism?

Dr. MIDTHUN. I think what I'd have to say is what the Institute of Medicine concluded is that the body of evidence neither——

Mr. BURTON. I want you to give me a yes or no. Can you tell me, can you say right now just flat out, just say can you tell me without any doubt whatsoever that the mercury in vaccines does not cause neurological problems or autism?

Dr. MIDTHUN. We can neither accept nor reject a causal relationship.

Mr. BURTON. So what you're saying is you cannot tell me that, you cannot say categorically, can you?

Dr. MIDTHUN. We don't know one way or the other.

Mr. BURTON. So why are you keeping something in there if you don't know one way or the other when you know that there's an epidemic of autism? If there's an epidemic of something, why do you keep it in there when you're not sure? Because every study I've seen flatly says you're not sure. You say there's—you can't say yea or nay.

Dr. MIDTHUN. I think you have to consider the benefit that vaccines confer. And there's a definite benefit from influenza vaccine and having an adequate supply of vaccine is very important.

Mr. BURTON. Let me followup on that then. Single-shot vials, does that need thimerosal?

Dr. MIDTHUN. No, they don't, but——

Mr. BURTON. Why do we have single shot vials?

Dr. MIDTHUN. There are a lot of manufacturing issues associated with switching over. You need much more filling capacity for the lines. You need a lot more other kinds of things that need to be introduced, so although it can be done and both Evans and Aventis Pasteur have started to introduce that, it is not something that at present they have the capacity to do in entirety.

Mr. BURTON. Let me ask you this: Do these pharmaceutical companies that produce these vaccines had, in the past, the ability to produce, and have they produced single-shot vials?

Dr. MIDTHUN. Yes, they do. Because that's how Evans and Aventis Pasteur is doing it to right now.

Mr. BURTON. How about all of the pharmaceutical companies? Do all of the pharmaceutical companies pretty much have the ability to produce single-shot vials?

Dr. MIDTHUN. You know, I couldn't speak to that categorically. I don't know. But I do know certainly in the case of Adventis Pasteur and Evans they do have the ability because they are doing that.

Mr. BURTON. Then why hasn't the FDA, to be on the safe side, knowing that we're having one in over 250, and in some cases, one in 150 children becoming autistic, and there's a growing body of evidence that thimerosal and mercury is causing that, why wouldn't you go down the cautious road instead of coming up with these additional studies that say well, we're not sure, we can't say yea or nay, why not go to single-shot vials?

Dr. MIDTHUN. Because we believe that the multi-dose vials continue to be safe and effective and that they speak to having enough supply of influenza vaccine, which serves a very important public——

Mr. BURTON. Let me end up by saying this. I'm a student. I studied at the Cincinnati Bible Seminary. I don't like to quote scripture very often, but there's none so blind as those that will not see. You just sit there and you keep saying over and over and over again that you think that there's not a real danger for having this mercury in these vaccines. There's been 1,500-plus articles written saying that there is a problem. We've got scientists from all over the world coming in here.

You saw a demonstration from a Canadian tape showing the impact of a minute amount of mercury in brain cells. And yet you continue to say well, we don't think that a very small amount of mercury—but you don't know because there's no study that you've put out, not one that says categorically that mercury in vaccines does not cause neurological problems. You can't tell me that today. You've hedged all over that issue. You guys continue to keep coming up here and making excuses. And I don't know why. Why not just get it out of there?

Dr. Weldon.

Mr. WELDON. Thank you, Mr. Chairman. I want to thank all of our witnesses in this panel for being here, and I didn't get an opportunity to thank the previous panel. Dr. Midthun, as I understand it, according to what you've said, thimerosal is in multi-dose vials of the influenza vaccine for a variety of reasons. We do currently recommend that children at risk receive the flu vaccine injection, is that correct?

Dr. MIDTHUN. That's correct.

Mr. WELDON. So though it is the case that thimerosal has been removed from all of the standard pediatric inoculations like MMR and DTPA, that some children may be getting thimerosal from the multi-dose vials that are still out there on the market, is that correct?

Dr. MIDTHUN. That's possible although I know that Aventis Pasteur, in speaking with them, they've tried very hard to target the trace thimerosal to the pediatric population, yes.

Mr. WELDON. Well, I would recommend to the FDA that you issue a recommendation that the single dose thimerosal free influenza vaccine be the vaccine used in the pediatric population.

Mr. BURTON. Would the gentleman yield?

Mr. WELDON. Yes.

Mr. BURTON. Because of the huge rise in Alzheimers and because they're putting thimerosal in the vaccines for flu for adults as well, and all the Members of Congress that get those shots are getting them, I wish you would amend that to take it out of all flu vaccines.

Mr. WELDON. Well, Mr. Chairman I was going to get to that issue.

What exactly is the problem, could you just explain it a little more detail, you know, if I were to offer an amendment on the Labor HHS appropriation bill, mandating that all thimerosal be removed from the market in the United States by a date certain, let's say July 2003 or December 31st, what is the problem with getting rid of this substance?

Dr. MIDTHUN. That is something that you know the manufacturers, you know, one would you have to say to them exactly——

Mr. WELDON. Manufacturing process?

Dr. MIDTHUN. It is that one has to remove the thimerosal from the product but then an even bigger issue is that you then have to fill multi-dose vials. And to fill multi-dose vials takes a lot more filling lung capacity than to fill multi-dose vials. So you have to have an infrastructure in place to be able to set that up. And I mean——

Mr. WELDON. So your concern is that such a mandate would result, if I understand your testimony correctly, in a possible shortage of available vaccine on the market.

Dr. MIDTHUN. That's correct. I believe that is the case.

Mr. WELDON. OK.

Dr. MIDTHUN. I don't believe that a transition can be made that quickly without creating quite a shortage. Let me just mention one other issue, and we've all been aware of vaccine shortages over these last couple of years is that Wyeth did announce that they are leaving the influenza vaccine market. So the market which previously had four manufacturers back in 2000, Parke Davis left that year, that had us down to three manufacturers and that was the first year where we experienced the influenza shortage.

Then last year we had somewhat of a delay there. Availability of the three remaining manufacturers worked very hard to make up for the shortfall of the fourth one who left. This year we'll be down to two. So I have concerns that taking that kind of a step, I don't believe it could be accomplished in that kind of a timeframe without leaving a vaccine shortage. I think one must consider the benefit that the vaccine conveys in terms of disease prevention against these other issues.

Mr. BURTON. Would the gentleman yield again? I'm sorry. The implication of your answer is that because of the problems with thimerosal and so forth, that's why they're not producing the flu vaccine, influenza vaccine again.

Dr. MIDTHUN. No. No. I do not know that. All I know——

Mr. BURTON. Isn't it true they are going to single-shot vials for measles; is that right? They're going to a nasal flu vaccine instead, is that not correct?

Dr. MIDTHUN. There is a license application in for a live attenuated nasally administered influenza vaccine. That vaccine—and I can disclose that because that is public knowledge—that vaccine is being developed by Metamune.

Mr. BURTON. Will that contain thimerosal?

Dr. MIDTHUN. No, that's a live, attenuated vaccine. That does not contain thimerosal.

Mr. BURTON. Thank you.

Mr. WELDON. I understand there is, under development, a nasal measles vaccine as well, is that correct?

Dr. MIDTHUN. You know, I don't know exactly what's been publicly disclosed here in open session. I can neither acknowledge or deny the existence of an IND. So I don't know what's been publicly disclosed in terms of any measles vaccines that might be under investigation or new drug application development.

Mr. WELDON. OK.

Mr. Foote, you know, I often wish I was Bill Gates and could just fund some research, I was originally made aware of Dr. Wakefield's work about 3 years ago when one of my constituents came in my office and contended that his child was well, developing normally with appropriate speech and eye contact, and then got the MMR and then proceeded to go down the tubes and got a second MMR years later and got even worse. And, you know, Dr. Wakefield's research was not expensive. You know, we throw billions of dollars around this town. What's the delay in getting this research done? And you know, we had a hearing back I think in July this fellow Kreigsman came in and on his own he has scoped all these kids and he's seen all the same exact findings that Dr. Wakefield has and he was real excited I've been talking to this guy, he's been biopsying all of these he's got all these little specimens and the IRP, Atlantic center hospital doesn't want to do the pathology on these things. They're just—I don't know if they're afraid or what, but you know, can't you find some way to just answer the doggone question so I don't to keep asking the same question year in year out. Am I going to be here in the 112th Congress asking NIH to answer me the question is Dr. Wake field a crack pot or is he on to something with the MMR?

Mr. FOOTE. So, after that hearing which I was either a witness or I was accompanying, I've already been up here a couple of times this year so I can't remember exactly which one that was I initiated a conversation with Dr. Kriegsman. I gave Dr. Kriegsman my business card, I told him to contact me because NIH would be interested in receiving a grant application in this area, especially from someone who it seemed had pilot data, and in his case, I believe a group of control subjects, material from control subjects which was—which would be critical to a well-designed study of the Wakefield kind of phenomenon.

So I did indeed have some phone conversations with him. We discussed this IRB issue. He was just at the point of interacting further with, I think—I think there was—there's some question in my mind about where exactly the IRB was located. I think this was part of the problem. But he explained some of these problems to me. I gave him whatever advice I could. I made clear that should he be able to resolve those difficulties, we would be very interested in receiving an application.

When I attended, the meeting annual meeting of the Autism Society of America——

Mr. WELDON. Go ahead, I'm sorry.

Mr. FOOTE. I was going to make one more quick point which is, when I attended the meeting of the annual meeting of the Autism Society of America in Indianapolis, I had a meeting with Dr. Wakefield and with some of his colleagues and so on. I made clear to them that I was willing to be a contact point within NIH for Dr. Wakefield or anybody else who was interested in submitting a grant application to——

Mr. WELDON. You know I'm not really interested in a grant to Dr. Wakefield. I would like somebody else to try to duplicate his work. And I think you could duplicate his work for $250,000 or less. And why can't we get that done?

Mr. FOOTE. All I'm telling you is when I meet somebody who—there were others——

Mr. WELDON. You're saying if somebody applies, you'll look very favorably.

Mr. FOOTE. I'll go further than that. I will help them figure out what the most effective—that is my job, I do it every day—what the most effective way is to approach NIH for getting funding for that research.

Mr. BURTON. Let me just ask a question. Dr. Kriegsman, now you've talked to him several times you said.

Mr. FOOTE. I talked to him, I think, twice on the phone about these.

Mr. BURTON. You told him what now?

Mr. FOOTE. I told him NIH, I would help him interface with NIH in terms of what kind of grant application to prepare, what kinds of review committees to institute——

Mr. BURTON. What else did he have to do before you could help him?

Mr. FOOTE. He told me that his problem was very similar to what Dr. Weldon indicated, it sounds like Dr. Weldon had some contact with him afterwards, also that he was having trouble with his institutional review for human subject studies.

Mr. BURTON. Down there at his hospital or his——

Mr. FOOTE. At his hospital or whatever IRP was responsible.

Mr. BURTON. Assuming that's the case and you realized the gravity of this situation, why doesn't our health agencies try to assist him in getting past that barrier? I mean, you know, it seems to me you say OK, if you can get past this barrier, and you know full well that there's a recalcitrance on the part of the Board of Governors of a hospital or health institution, it seems to me you would say, hey, this is significant enough that we really ought to help this guy instead of just saying when you get past that, give us a call. Can't you do something like that? Can't you guys initiate some help for some of these people?

Mr. FOOTE. We have in terms of human subjects, animal subjects, ethical issues and so on, the model that is in place is that the grantee institutions assume responsibility for those issues. And NIH tries not to mandate or micromanage those issues at grantee institutions.

Mr. BURTON. So if a person——

Mr. FOOTE. There is a limit on me intruding or anybody else intruding into those types of considerations.

Mr. BURTON. Let me give you a hypothetical. Let's say we were going to have, in some part of the country, let's say major outbreak of smallpox. And let's say that we had an institution where a doctor or scientist had some kind of an answer to the problem. And he said he was running into because of insurance purposes or some other legal reason his board of directors from being able to get their support for this IRB. So you would say what let the epidemic spread or what would you do?

Mr. FOOTE. Well, I would offer an alternative.

Mr. BURTON. What's the alternative you're offering him?

Mr. FOOTE. He never called me back?

Mr. BURTON. Well, I'm telling you he's going to call you back, and I hope.

Mr. FOOTE. That's just fine. This is what program staff at NIH do is help investigators in face with our organization.

Mr. BURTON. Does he know that you would help him find an alternative?

Mr. FOOTE. I think I had, including at the hearing here, I think I had three or four very cordial conversations with him and encouraged him.

Mr. WELDON. I just want to clarify with Dr. Foote exactly what's going on. He's done the endoscopies, he's biopsied the kids, he's got the specimens, he wanted to do duplicate the work that Dr. O'Leary did looking for the presence of measles virus RNA in the lymph follicles of these kids, and that's the nature of the patho physiologic conjecture that they're engaged in, and the IRB Atlantic cell said no, we don't want to go there, we don't want to mess with this.

I just want to make it very, very clear. My area of concern is this: Is when you leave all these questions out there unanswered, it creates a lot of uncertainty. And the British have not handled this very well and they still continue not to handle it very well. And that we just have an open dialog and just absolutely pursue the data, it's in the best interest of the program in making sure the kids continue to get vaccinated. And I don't know what it will take to get the answers to this question, but I'm certainly ready to work with you.

Mr. Chairman, I got to go apologize. I'd love to linger.

Mr. BURTON. God bless you, my son, go in peace. But let me just say to Dr. Foote, you will be getting a call from him in the next couple of days, I promise you that. And I probably will be on the phone with you in a conference call. Thanks, Dr. Weldon.

I have to put on my specs here because vanity prohibits me from wearing them all the time like Cyrano de Bergerac, you have to read about him. Here is an e-mail, and this e-mail is from who? See, I want to read to you an e-mail we got yesterday from a father of an autistic child. Ray Gallup's son, he's 17, he's vaccine injured and an autistic child as a result. 17 years old.

> Our family is living in hell. With our 17-year-old son Eric, who is 6 feet tall and 150 pounds. Now, imagine 6 feet tall 150 pounds like that boy you saw on television or on the monitor a while ago. He attacked Helen, Julie my daughter, and myself. He head butted Julie and bit my wife on the head. Eric bit one of my fingers.
>
> This isn't the first time and it's getting worse. We have to help and I'm afraid for the safety of our family and our son. Eric was like he was 6 foot 5 and 300 pounds on Sunday when he had his tantrum. I held him down but he tried to bite me and kick and scratch me. I was so exhausted I couldn't breathe and I thought I would have a heart attack. When we closed the doors to lock ourselves from Eric—lock ourselves from Eric—he kicked on the door breaking some of the wood.
>
> I don't know what to do any more short of calling the police. We're at our wit's ends. This is our lot in life. We're trusting the medical profession that vaccines are safe. We're paying a bitter price for that trust. It is hard to have any holiday feelings when we see what has happened to our son and our family.
>
> Again, I'm sorry I couldn't attend but we are under siege.

You know, Dr. Midthun, and Dr. Foote, and Dr. Portier, when you hear those stories, doesn't it bother you a little bit and you keep telling us you come up here week after week, month after month, year after year saying, well, mercury doesn't cause that. But when we read your reports it doesn't say that. It doesn't tell us anything. It says well, we're not sure. So you take the position since there's no scientific evidence for sure that the mercury is causing it, that we should go ahead and leave it in there or have been leaving it in there.

But you don't take the other side, which is the side that errs on the side of safety. Let's go to these pharmaceutical companies and say OK, we know it's going to cost a little more for single-shot vials, but we want you to do it. We want to recall, recall all of the vaccines that contain mercury because it is a toxic substance, and we don't know all the answers. And until we do know all the answers, we want to err on the side of safety so we don't have anymore 6 foot 5 kids beating the heck out of their parents, biting their father, kicking in doors and injuring the mother and sister. But that's going to happen more and more.

You know my grandson, who's autistic, is going to be 6 foot 10 according to the doctors. My father was 6 foot 8, his father—his grandfather on the other side was about 6 foot 8. So he's going to be a tall kid. Can you imagine when he's 16 years old trying to control him if he goes out of control? What are we going to do? What are all these families going to do? And yet we don't have a vaccine injury compensation fund that's responsive to these people. The language that was put in the homeland security bill blocks an avenue through the courts. And these families continue to fight this hardship with their own money because they have no place to go, and you continue to put, you continue to let this substance in there. I just cannot understand it. I just don't understand it.

I have one question for you, Dr. Portier, and then we'll submit some questions for the records that I hope you'll answer for me. Dr. Portier, does the study recently published in The Lancet identify the effects of mercury on infants who are vaccinated with thimerosal?

Does the study recently published in The Lancet identify the effects of mercury on infants who are vaccinated with thimerosal?

Dr. PORTIER. No.

Mr. BURTON. It does not. Are you familiar with the CDC's vaccine safety data project evaluating thimerosal containing vaccines in children that found a weak signal between the receipt of these vaccines and neurological developmental delays and the attention deficit disorder?

Dr. PORTIER. Not familiar enough with the study to give you any intelligent comment.

Mr. BURTON. Has the NIEHS and the NIH conducted any further analysis of the VSD data base?

Dr. PORTIER. No, we have not, to my knowledge.

Mr. BURTON. Has the NIEHS evaluated why some children seem to hold on to mercury in their brains and their bodies? Or why some hol onto heavy metals rather than flush it from their bodies? If not, why not?

Dr. PORTIER. That is one of the issues specifically for mercury and that's being looked at at our centers program. That's part of the research agenda of the National Toxicology Program and for other metals, that is certainly part of our research agenda.

Mr. BURTON. OK. Well, thank you. I think I'm going to submit questions to you. One more thing, and this is very important. I hope you will join with me as health professionals in urging the President to have a White House conference on autism which will bring parents in, scientists who have differing points of view as well as people from our health agencies in to discuss the problems with autism, what people go through, what the causes are and so on and so forth. This is such an epidemic, gone from 1 in 10,000 to more than 1 in 250 that it's something that we can't hide anymore.

I'd like for to you join me in asking the White House to make this a real focal point by having this conference on autism. And I guess you can't probably give me an answer until you talk to your superiors, but I'm making that official request, an official request. I hope you'll do that and get back to us.

Let me conclude by saying we will continue on with this subject. You have gotten mercury out of a lot of the vaccines. I berated you a lot in the past and a little bit today because it's still in some. But we have moved in the right direction. It's a shame that it has taken this long to get it out as much as we have. But I can tell you there's going to be a lot more Congressmen very concerned about there because we're start together tell all of them that when they get their flu shot, they're getting mercury in them. And that there's a growing body of evidence that mercury in vaccines may be a major cause of Alzheimers.

And when I tell my colleagues that, there's going to be more and more of them wanting to raise Cain about this. And I know you don't want to have to deal with you know another 200 Dan Burtons, my God, that would be something even I wouldn't want to deal with. So I hope that you'll take this to heart and I hope we don't have to have too many more hearings like this, but we will if we don't see some real change and see some studies on this.

With that we'll submit some questions to you for the record. I hope you'll answer them. Thank you for being here. We stand adjourned.

[Whereupon, at 5:02 p.m., the committee was adjourned.]

[The prepared statement of Hon. Wm. Lacy Clay, additional information submitted for the hearing record, and a complete set of exhibits follow:]

Statement of the
Honorable William Lacy Clay
Before the
Government Reform Committee
Tuesday, December 10, 2002

"Vaccines and the Autism Epidemic: reviewing the Federal government's Track Record and Charting a Course for the Future"

Thank you for yielding, Mr. Chairman, Autism Spectrum Disorder (ASD) is a disorder that knows no racial, ethnic or social boundaries. There are estimates as high as 1.5 million possible Americans that are affected by this debilitating disorder. Current funding levels for research by the National Institutes of Health are around $56 million and $11 million by the Center for Disease Control. This should be viewed only as a start, not a finish to eradicating this disorder.

After pursuing background information, discourse, and testimony on this issue for several months, I believe the public is much more familiar with the issue of Autism and its possible treatments largely because of your leadership on this important subject, Mr. Chairman.

Today's hearing focuses on the relationship between vaccines and the Autism epidemic and a review of the federal government's record of accomplishment in minimizing the disorder's effect. I am interested in hearing from the representatives of the Food and Drug Administration (FDA) and the Center for Disease Control (CDC). The research their agencies have compiled can assist members of this committee to better understand where we are and most of all where we have to go regarding funding and the possible over-vaccination of our children. I am equally interested in hearing from Dr. Andrew Wakefield and his theory concerning the relationship between Autism and the Measles, Mumps, and Rubella

(MMR) vaccine and its effects. However, beyond that understanding, I want to have clarification today from the CDC as to why it cannot under the Freedom of Information Act (FOIA) release the data on the link between thimerosal exposure and development delays. The Vaccine Safety Datalink (VSD) project has been in place since 1990. In that time, I am certain that the (VSD) project has compiled the data necessary to advance substantially the research on Autism Spectrum Disorder (ASD). The immediate release of this information could make a real difference in the research effort to better treat this disorder.

I also would like clarification on the CDC and its relaxed relationship with health maintenance organizations (HMO's). It is my understanding that HMO's are required under law to provide data to the VSD project. Whom is the CDC protecting and why are its representatives running interference for the HMO's? I hope that we will find out the answers to these questions and more in today's hearing. Finally, I want to commend you, Mr. Chairman, for writing the President in calling for a White House Conference on Autism. I hope that the President feels compelled to increase the necessary funding and to direct the NIH and CDC to work towards finding a suitable treatment as well. Mr. Chairman, I ask unanimous consent to submit my statement into the record.

The Journal

- Current Issue
  - Contents in full
  - Talking points
  - Original research
  - WHO Director-General election
  - News
  - Editorial and review
  - Correspondence
  - Uses of error
  - Clinical picture
  - Dissecting room
- Supplements
- Back Issues

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30 November 2002

« »

Articles

Mercury concentrations and metabolism in infants receiving vaccines containing thiomersal: a descriptive study

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Summary
Introduction
Methods
Results
Discussion
References

Summary

Background Thiomersal is a preservative containing small amounts of ethylmercury that is used in routine vaccines for infants and children. The effect of vaccines containing thiomersal on concentrations of mercury in infants' blood has not been extensively assessed, and the metabolism of ethylmercury in infants is unknown. We aimed to measure concentrations of mercury in blood, urine, and stools of infants who received such vaccines.

Methods 40 full-term infants aged 6 months and younger were given vaccines that contained thiomersal (diptheria-tetanus-acellular pertussis vaccine, hepatitis B vaccine, and in some children *Haemophilus influenzae* type b vaccine). 21 control infants received thiomersal-free vaccines. We obtained samples of blood, urine, and stools 3-28 days after vaccination. Total mercury (organic and inorganic) in the samples was measured by cold vapour atomic absorption.

Findings Mean mercury doses in infants exposed to thiomersal were 45·6 μg (range 37·5-62·5) for 2-month-olds and 111·3 μg (range 87·5-175·0) for 6-month-olds. Blood mercury in thiomersal-exposed 2-month-olds ranged from less than 3·75 to 20·55 nmol/L (parts per billion); in 6-month-olds all values were lower than 7·50 nmol/L. Only one of 15 blood samples from controls contained quantifiable mercury. Concentrations of mercury were low in urine after vaccination but were high in stools of thiomersal-exposed 2-month-olds (mean 82 ng/g dry weight) and in 6-month-olds (mean 58 ng/g dry weight). Estimated blood half-life of ethylmercury was 7 days (95% CI 4-10 days).

Interpretation Administration of vaccines containing thiomersal does not seem to raise blood concentrations of mercury above safe values in infants. Ethylmercury seems to be eliminated from blood rapidly via the stools after parenteral administration of thiomersal in vaccines.

Lancet 2002; **360:** 1737-41

See Commentary
▲ top

Introduction

Thiomersal is a preservative used in vaccines routinely administered to infants and children. Its antimicrobial activity is due to small amounts of ethylmercury; the usual dose of paediatric vaccine contains 12·5-25 μg of mercury.[1-3] When vaccines containing thiomersal are administered in the recommended doses, allergic reactions have been rarely noted, but no other harmful effects have been reported.[4] Massive overdoses from inappropriate use of products containing thiomersal have resulted in toxic effects.[5-9]

Mercury occurs in three forms: the metallic element, inorganic salts, and organic compounds (eg, methylmercury, ethylmercury, and phenylmercury). The toxicity of mercury is complex and dependent on the form of mercury, route of entry, dosage, and age at exposure. Mercury is present in the environment in inorganic and organic forms, and everyone is exposed to small amounts.[10,11] The main route of environmental exposure to organic mercury is consumption of predatory fish, especially shark and swordfish. A 6-ounce can of tuna contains 2-127 μg (average 17 μg) of mercury.[12] Freshwater fish (eg, walleye, pike, muskie, and bass) can also contain high concentrations of mercury.

Most of the toxic effects of organic mercury compounds take place in the central nervous system, although the kidneys and immune system can also be affected.[10,11,13] Organic mercury readily crosses the blood-brain barrier, and fetuses are more sensitive to mercury exposure than are children or adults. Data about potential differences in toxicity between ethylmercury and methylmercury are few. Both are associated with neurotoxicity in high doses; in-utero poisoning with methylmercury causes problems that are similar to cerebral palsy. Findings about the effect of low-dose methylmercury exposure on neurodevelopment in infants are contradictory.[14,15] In-utero exposure could be related to subtle neurodevelopmental effects (eg, on attention, language, and memory) that can be detected by sophisticated neuropsychometric tests-- although the conclusion is confounded by concomitant ingestion of polychlorinated biphenyls in the patients investigated.[14,15]

No toxic effects of low-dose exposure to thiomersal in children have been reported.[3] The effect of the small amounts of mercury contained in vaccines on concentrations of mercury in infants' blood has not been extensively assessed, and the metabolism of ethylmercury in infants is unknown. We aimed to assess concentrations of mercury in full-term infants after administration of routine vaccinations according to the schedule used in the USA, and to obtain additional information about the presence of mercury at other body sites including urine and stool. Samples of hair and breast milk were also obtained from some mothers of infants participating in the study.

▲ top

Methods

Study populations

We studied two groups of full-term infants who differed in their history of exposure to vaccines containing thiomersal. Infants in the exposure group were recruited at the Elmwood Pediatric Group, a large paediatric practice in Rochester, NY, USA, where vaccinations with thiomersal preservative were routinely given. 20 infants aged 2 months and 20 aged 6 months were studied at this practice to obtain information about the range of total thiomersal exposures likely to take place during infancy. The control group consisted of 21 infants who did not receive vaccines containing thiomersal and were recruited from the National Naval Medical Center, Bethesda, MD. All the infants were recruited during routine well-child examination and vaccination visits by the investigators (between November, 1999 and October, 2000). Written informed consent was obtained from parents for all procedures.

Vaccines

Vaccines containing thiomersal that were given to infants in the exposure group included Tripedia (diphtheria-tetanus-acellular pertussis vaccine; Aventis Pasteur, Swiftwater, PA; 0·01% thiomersal, 25 μg mercury per dose) Engerix (hepatitis B vaccine; GlaxoSmithKline, Rixensart, Belgium; 0·005% thiomersal, 12·5 μg mercury per dose), and in some children HibTITER (*Haemophilus influenzae* type b conjugate vaccine, Wyeth-Lederle, Pearl River, NY, USA; 0·01% thiomersal, 25 μg mercury per dose). Vaccines administered to the control group included Infanix (diptheria-tetanus-acellular pertussis vaccine; GlaxoSmithKline, Rixensart, Belgium), Recombivax HB (hepatitis B vaccine; Merck, West Point, PA, USA), and ActHIB (*Haemophilus influenzae* b conjugate vaccine, Aventis Pasteur, Swiftwater, PA, USA).

Procedures

We obtained vaccination histories--including type of vaccine, manufacturer, lot number, and dates of administration--from the medical records. In the exposure group, we obtained samples of heparinised whole blood, stool, and urine, during a visit 3-28 days after vaccination. Blood and urine were kept at 4°C, and stools were frozen until assessment. Urine was sampled by use of a urine bag at the clinic, and stool was taken from a diaper (nappy) provided by the parent. Whole blood and urine were obtained from the control children. At both sites, we obtained at least 50 hairs from the mother by cutting at the base near the scalp in the occipital area, to assess potential transplacental exposure of infants to mercury. Additionally, several samples of breastmilk or formula were obtained from mothers of infants at Elmwood Pediatric Group, as well as stool samples from a few infants who were not exposed to thiomersal.

We measured total mercury in all samples (and inorganic mercury in stool samples) by cold vapour atomic absorption as previously described.[16,17] The limit of reliable quantitation in this assay ranged between 7·50 nmol/L and 2·50 nmol/L, dependant on sample volume.

Population pharmacokinetic calculations

To estimate the half-life of thiomersal mercury in the blood, we developed a prediction model for the expected concentrations of mercury in blood for half lives of mercury ranging from 1 day to 45 days, on the basis of bodyweight of the infant, the doses of thiomersal administered, and the times between the individual doses of thiomersal and when the blood was obtained. To do these calculations, we assumed that 5% of the mercury dose was distributed to blood,[7] that blood volume represented about 8% of the infant's bodyweight, and that elimination of mercury from blood followed a single-compartment model with first-order kinetics. For each possible half-life between 1 and 45 days, we then calculated the difference between the predicted and actual recorded concentrations in blood for each infant. Only measurements within the range of reliable quantitation were used in these calculations.

The best estimate of the blood half-life of mercury was judged to be the hypothetical half-life, which resulted in the smallest difference between predicted and observed values. We constructed a 95% CI based on a likelihood ratio for this estimate with the assumption that errors from the decay model were independent, additive, and normally distributed. The 95% confidence limits were the points where the curve crossed the minimum sum of squares multiplied by $1+\chi^2(1)/(n-1)$ where n is the number of data points and $\chi^2(1)$ is the upper 5% point of the χ^2 distribution on one degree of freedom.

Statistical analysis

Because this was a descriptive study we did no formal calculations for sample size. Student's *t* test and Fisher's exact test were used to compare results for the exposure and control group, with $p \leq 0{\cdot}05$ judged to be significant.

Role of the funding source

The sponsors of the study approved the study design but had no other involvement in the in study design, data collection, data analysis, data interpretation, or writing of the report.

▲ top

Results

61 infants were enrolled in this study (table). Among infants aged 2 months in the exposure group, samples were taken from eight within 7 days of vaccination, from five between 8 and 14 days after vaccination, and from seven between 15 and 21 days after vaccination. Among 6-month-old infants in the exposure group, samples were taken from seven between 4 and 7 days after vaccination, from eight between 8 and 14 days after vaccination, and from five between 15 and 27 days after vaccination. Samples were obtained from infants in the control group at regularly scheduled visits at 2 or 6 months of age. All children remained healthy throughout the study and during 24-36 months of follow-up.

	Infants aged 2 months		**Infants aged 6 months**	
	Thiomersal-exposed (n=20)	Controls (n=11)	Thiomersal-exposed (n=20)	Controls (n=10)
Bodyweight (kg)				
Mean (range)	5·3 (4·0-6·4)	NR	8·1 (6·7-10·6)	NR
Total mercury exposure (µg)*				
Mean (range)	45·6 (37·5-62·5)	0	111·3 (87·5-175·0)	0
Blood mercury				

Blood mercury (nmol/L)				
Number of samples tested	17	8	16	7
Number with mercury in range	12	1	9	0
Mean (SD)†	8·20 (4·85)	4·90	5·15 (1·20)	..
Median (IQR)†	6·15 (4·60-10·85)	4·90	5·30 (4·55-6·10)	..
Range†	4·50-20·55	..	2·85-6·90	..
Urinary mercury (nmol/L)				
Number of samples tested	12	6	15	8
Number with mercury in range	1	0	3	0
Mean (SD)†	3·8‡	..	5·75 (1·05)	..
Median (range)†	3·8‡	..	6·2 (4·55-6·45)	..
Stool mercury (ng/g dry weight)				
Number of samples tested	12	NT	10	NT
Number with mercury in range	12	..	10	..
Mean (SD)†	81·8 (40·3)	..	58·3 (21·2)	..
Median (IQR)†	83·5 (47·0-121·3)	..	58·0 (42·0-68·5)	..
Range†	23·0-141·0	..	29·0-102·0	..

NR=Not recorded. NT=not tested. *Via vaccination. †All calculations done only with samples within range of accurate quantitation. ‡Only one value so SD and range are not applicable.

Concentrations of mercury in blood, urine, and stool of infants who received vaccines containing thiomersal and those who did not

Sufficient volumes of blood (≥1 mL) for the measurement of mercury by the atomic absorption technique were obtained from 17 infants aged 2 months and 16 aged 6 months in the exposure group. Mercury concentrations were below the range of reliable quantitation in five of 17 blood samples from 2-month-olds, and seven of 16 blood samples from 6-month olds (p=0·48). The mean concentration of blood mercury in samples with quantifiable mercury was higher in 2-month-olds than in 6-month olds (difference 3·05 nmol/L, 95% CI 0·03-1·24, p=0·06), but was low in both these groups (table). Sufficient blood volumes for measurement of mercury were obtained from 15 infants in the control group, including eight aged 2 months and seven aged 6 months. Blood mercury was below the level of reliable quantitation in seven of the eight samples from the 2-month-olds and in all seven samples from 6-month-olds. The only detectable value from the control group was 4·65 nmol/L.

Overall, mercury concentrations were below the range of quantitation in 12 of 33 samples from thiomersal-exposed infants and in 14 of 15 unexposed infants (p=0·04). The highest level of blood mercury detected in any infant in this study was 20·55 nmol/L, which was measured 5 days after vaccination in a 2-month-old infant weighing 5·3 kg, who had received vaccines (Tripedia and Engerix B) containing a total dose of 37·5 μg mercury. The relation between time between vaccination and sampling and the concentration of mercury in the blood in the exposed group is shown in figure 1. Although mercury concentrations were uniformly low, the highest levels were recorded soon after vaccination.

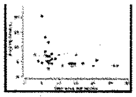

Figure 1: **Blood mercury concentrations in infants aged 2 months (diamonds) and 6 months (squares) by time of sampling**

Filled symbols represent measured values and open symbols represent samples at the limit of quantitation, either 7·50 nmol/L, 3·75 nmol/L, or 2·5 nmol/L, dependent on sample volume.

Mercury was undetectable in most of the urine samples from the infants in this study. Only one of 12 urine samples from 2-month-olds, and three of 15 from 6-month-olds in the exposure group, and none of the 14 samples from the controls, contained detectable mercury. The highest concentration of urinary mercury detected was 6·45 nmol/L, in a 6-month old infant in the exposure group (table).

Stool samples were collected from infants in the exposure group. All of the stool samples from infants who received thiomersal-containing vaccines had detectable mercury, with concentrations in stools from 2-month-old infants slightly higher than those in 6-month-olds (p=0·098, table). As expected, most of the mercury in stools was inorganic. Stool samples were not obtained from control infants; therefore, to determine whether dietary intake could contribute to the mercury content of stools, we also obtained samples from nine infants at Elmwood Pediatric Group who were age-matched with the infants in the exposure group and were not exposed to vaccines containing thiomersal. The mean mercury concentration in the stools of these infants was 22 ng/g dry weight (SD 16), which was significantly lower (p=0·002) than the mean of the samples collected from thiomersal-exposed infants.

Amounts of mercury measured in maternal hair are shown in figure 2. The mean concentration of hair mercury in mothers of the exposure group was 0·45 µg/g hair, whereas the mean amount in mothers of the control infants was 0·32 µg/g (p=0·22). Eight mothers of infants in the 6-month-old cohort provided breast milk samples. Concentrations of mercury in these samples were low (mean=0·30 µg/g, range 0·24-0·42 µg/g).

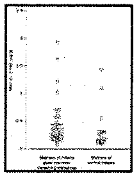

Figure 2: **Mercury concentrations in hair from mothers of infants**

Bar represents mean concentration of mercury in maternal hair.

We estimated the half-life of mercury in blood after vaccination to be 7 days, since this result gave the smallest difference between the expected and recorded (measured) concentration (figure 3). The 95% CI around this estimate was 4-10 days. The half-life estimate was very similar when only measurements in 2-month-olds (7 days, 95% CI 4-11) or 6-month-olds (5 days, 3-9) were included, suggesting that the rate of elimination of thiomersal mercury from blood was similar in both age-groups.

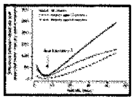

Figure 3: **Estimated blood half-life of mercury in infants who were exposed to thiomersal**

Lines represent sum of square of differences between observed concentrations of blood mercury (nmol/L) and those predicted for every individual infant on the basis of bodyweight and time of sampling, with a series of hypothetical half-lives shown on x axis. Arrow shows point with lowest value for squared difference, indicating best estimate for serum half-life.

▲ top

Discussion

We have shown that very low concentrations of blood mercury can be detected in infants aged 2-6 months who have been given vaccines containing thiomersal. However, no children had a concentration of blood mercury exceeding 29 nmol/L (parts per billion), which is the concentration thought to be safe in cord blood;[18] this value was set at ten times below the lower 95% CI limit of the minimal cord blood concentration associated with an increase in the prevalence of abnormal scores on cognitive function tests in children. Blood mercury concentrations indicate concentrations in organs well.[18]

Although our study was not designed as a formal assessment of the pharmacokinetics of mercury, we did obtain samples of blood at various time points after exposure. Assessment of these samples suggested that the blood half-life of ethylmercury in infants might differ from the 40-50 day half-life of methylmercury (range 20-70 days) in adults and breastfeeding infants.[10,19] The concentrations of blood mercury 2-3 weeks after vaccination noted in our study were not consistent with such a long half-life, but suggested a half-life of less than 10 days. However, this conclusion is based on several assumptions and a very simple model, and does not take into account the fact that at least some of the mercury detected in the blood of the infants in this study is likely to have been derived from exposures other than vaccination. Because of the short period between vaccination and sampling, the findings of Strajich and colleagues[20] could be consistent with either a 6-day or 40-day half-life, but are otherwise consistent with the assumptions made in our model. Because we expected a 45-day half-life on the basis of methylmercury pharmacokinetics, the first blood samples were obtained 3 days after vaccination. Blood samples taken in the first 72 hours after vaccination, stool samples obtained every 24 h, and samples from premature newborn babies (weighing≥2000 g) given a birth dose of hepatitis B vaccine would have helped us to reach stronger conclusions. Thus, additional studies of the pharmacology of thiomersal in infants are underway.

At the times tested after vaccination, mercury excretion in urine in our study population was low. By contrast, concentrations of mercury in stool were high, and combined with the finding that stool mercury concentrations in infants who were not exposed to thiomersal were significantly lower is consistent with the hypothesis that the gastrointestinal tract represents a possible mode of elimination of thiomersal mercury in infants.

Overall, the results of this study show that amounts of mercury in the blood of infants receiving vaccines formulated with thiomersal are well below concentrations potentially associated with toxic effects. Coupled with 60 years of experience with administration of thiomersal-containing vaccines, we conclude that the thiomersal in routine vaccines poses very little risk to full-term infants, but that thiomersal-containing vaccines should not be administered at birth to very low birthweight premature infants. Decisions about the elimination of thiomersal from these vaccines must balance the potential benefit of reduced exposure to mercury against the risks of decreased vaccine coverage because of higher costs, the risk of sepsis in recipients because of bacterial contamination of preservative-free formulations, and the risks of exposure to alternative preservatives that might replace thiomersal.

Conflict of interest statement

None declared.

Contributors

M Pichichero and J Treanor contributed to the study conception and design; obtained, assessed, and interpreted data; drafted and revised the manuscript; and provided statistical expertise and supervision. E Cernichiari contributed to analysis and interpretation of data, revision of the manuscript, and technical support. J Lopreiato contributed to revision of the manuscript, and obtained data.

Acknowledgments

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▲ top

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▲ top

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▲ **top**

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- Current Issue
  Contents in full
  Talking points
  Original research
  WHO Director-General election
  News
  Editorial and review
  Correspondence
  Uses of error
  Clinical picture
  Dissecting room
- Supplements
- Back Issues

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Home ➤ The Journal ➤ Current Issue ➤ Editorial and review

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30 November 2002

« »

Commentary

Mercury in vaccines--reassuring news

The mass media and alternative-medicine publications increasingly report that exposure to and the build-up of mercury within the body is associated with chronic ill-health, particularly conditions such as myalgic encephalitis. Mercury is widespread in the environment; it is found naturally in rocks, soils, and plants and as a contaminant in air, water, and food. The element is used a lot in the electrical industry, and in many domestic products, including paints, pesticides, fabric softeners, waxes, and polishes. Mercury is often used as a preservative in vaccines, skin creams, cosmetics, and other medications. Mercury is the major component of dental amalgams and there is a growing lobby against its use.[1] Everyone is exposed to small amounts of mercury as elemental metallic vapour from dental amalgams or organic mercury from fish, sea foods, and vaccines, or to inorganic salts from other food stuffs, water, and air. Faecal excretion is the major route of elimination of inorganic or organic mercury.

Elemental mercury from amalgams is lipid-soluble and freely passes through cell membranes.[2] By contrast, organic and inorganic mercury from the diet and other sources are charged and must be complexed with other counter-ions or low-molecular-weight sulphur compounds to pass through cell membranes. The major targets in proteins susceptible to binding of metals, including mercury, are the sulphydryl group of cysteine and the iminonitrogen of histidine. The aromatic ring nitrogens of the nucleotide bases form mercury complexes, with thymine and uracil being more reactive than cytosine, guanine, and adenine.[3,4] The most abundant single nucleophile reactant is the antioxidant glutathione, typically present at concentrations of 5 mmol/L in cells, serum, and bile.[5] Glutathione mops up ionised mercury derived from oxidation of elemental mercury and from organic and inorganic mercury. There may be an inverse relation between the concentration of intracellular glutathione and mercury toxicity.[6] Once bound to glutathione, mercury can leave the cell and circulate freely in serum and lymph from where it can be deposited in other organs and tissues. Glutathione-complexed mercury is eventually eliminated via the kidney or downloaded via bile into the intestinal lumen from where it is excreted in faeces. After mercury is released from tissues, faecal excretion is the predominant route for elimination.

In this issue of *The Lancet*, Michael Pichichero and colleagues investigate mercury levels and excretion in infants receiving vaccines containing thiomersal (ethyl mercury). Little is known about the harmful effects of mercury in infants and children and at what level these effects occur. At between 12·5 and 25 mg mercury per vaccine dose, the infants may be receiving over 100 mg ethyl mercury in the first 6 months of life. Pichichero and colleagues show that the levels in blood are much lower than the prescribed limits and that much of the ethyl mercury appears to be eliminated rapidly in faeces. This study gives comforting reassurance about the safety of ethyl mercury as a preservative in childhood vaccines.

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A POPULATION-BASED STUDY OF MEASLES, MUMPS, AND RUBELLA VACCINATION AND AUTISM

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ABSTRACT

Background It has been suggested that vaccination against measles, mumps, and rubella (MMR) is a cause of autism.

Methods We conducted a retrospective cohort study of all children born in Denmark from January 1991 through December 1998. The cohort was selected on the basis of data from the Danish Civil Registration System, which assigns a unique identification number to every live-born infant and new resident in Denmark. MMR-vaccination status was obtained from the Danish National Board of Health. Information on the children's autism status was obtained from the Danish Psychiatric Central Register, which contains information on all diagnoses received by patients in psychiatric hospitals and outpatient clinics in Denmark. We obtained information on potential confounders from the Danish Medical Birth Registry, the National Hospital Registry, and Statistics Denmark.

Results Of the 537,303 children in the cohort (representing 2,129,864 person-years), 440,655 (82.0 percent) had received the MMR vaccine. We identified 316 children with a diagnosis of autistic disorder and 422 with a diagnosis of other autistic-spectrum disorders. After adjustment for potential confounders, the relative risk of autistic disorder in the group of vaccinated children, as compared with the unvaccinated group, was 0.92 (95 percent confidence interval, 0.68 to 1.24), and the relative risk of another autistic-spectrum disorder was 0.83 (95 percent confidence interval, 0.65 to 1.07). There was no association between the age at the time of vaccination, the time since vaccination, or the date of vaccination and the development of autistic disorder.

Conclusions This study provides strong evidence against the hypothesis that MMR vaccination causes autism. (N Engl J Med 2002;347:1477-82.)

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IT has been suggested that the measles, mumps, and rubella (MMR) vaccine causes autism.[1-4] The widespread use of the MMR vaccine has reportedly coincided with an increase in the incidence of autism in California,[5] and there are case reports of children in whom signs of both developmental regression and gastrointestinal symptoms developed shortly after MMR vaccination.[1] Measles virus has been found in the terminal ileum in children with developmental disorders and gastrointestinal symptoms but not in developmentally normal children with gastrointestinal symptoms.[6] The measles virus used in the MMR vaccine is a live attenuated virus that normally causes no symptoms or only very mild ones. However, wild-type measles can infect the central nervous system and even cause postinfectious encephalomyelitis, probably as a result of an immune-mediated response to myelin proteins.[7-9]

Studies designed to evaluate the suggested link between MMR vaccination and autism do not support an association, but the evidence is weak and based on case-series, cross-sectional, and ecologic studies. No studies have had sufficient statistical power to detect an association, and none had a population-based cohort design.[10-16] The World Health Organization and other organizations have requested further investigation of the hypothetical association between the MMR vaccine and autism.[2,17-20] We evaluated the hypothesis in a cohort study that included all children born in Denmark in 1991 through 1998.

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METHODS

Study Design

We designed a retrospective follow-up study of all children born in Denmark during the period from January 1, 1991, to December 31, 1998. The cohort was established on the basis of data obtained from the Danish Civil Registration System and five other national registries.

All live-born children and new residents in Denmark are assigned a unique personal identification number (a civil-registry number), which is stored in the Danish Civil Registration System together with information on vital status, emigration, disappearance, address, and family members (mother, father, and siblings).[21] The registry is updated once a week, and all changes in the stored information are reported to the registry according to established legal procedures. The civil-registry number is used as the link to information at the individual level in all other national registries. This system provides completely accurate linkage of information between registries at the individual level.

We determined MMR-vaccination status on the basis of vaccination data reported to the National Board of Health by general practitioners, who administer all MMR vaccinations in Denmark. The general practitioners are reimbursed by the state on the basis of these reports. We retrieved information on vaccinations from 1991 through 1999. The MMR vaccine was introduced in Denmark in 1987, and the single-antigen measles vaccine has not been used. The MMR vaccine used in Denmark during the study period was identical to that used in the United States and contained the following vaccine strains: Moraten (measles), Jeryl Lynn (mumps), and Wistar RA 27/3 (rubella).

The national vaccination program recommends that children be vaccinated at 15 months of age and again at 12 years. No change was made in the program during the study period. We obtained information on MMR vaccination at 15 months of age, since only this exposure is relevant to the end point under study. Since the vaccination data are transferred to the National Board of Health once a week, we chose Wednesday as the day of vaccination. When the vaccination information was recorded with the child's own civil-registry number, the information was directly linked with other registries. Before 1996, in most cases the vaccination information and the age of the child were recorded with the civil-registry number of the accompanying adult; we used information from the Danish Civil Registration System to identify the link from the accompanying adult to the child. Thus, 98.5 percent of the children were identified with the use of the child's civil-registry number or the civil-registry number of the mother or father and the age of the child at vaccination. The remaining 1.5 percent of children were identified on the basis of additional information from the Danish Civil Registration System on other relatives and information on the address at the time of vaccination.

Information about diagnoses of autism was obtained from the Danish Psychiatric Central Register, which contains information on all diagnoses received by patients in psychiatric hospitals, psychiatric departments, and outpatient clinics in Denmark.[22] In our cohort, 93.1 percent of the children were treated only as outpatients, and 6.9 percent were at some point treated as inpatients in a psychiatric department. All diagnoses were based on the *International Classification of Diseases, 10th Revision* (ICD-10), which is similar to the 4th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) with regard to autism.[23-26] In Denmark, children are referred to specialists in child psychiatry by general practitioners, schools, and psychologists if autism is suspected. Only specialists in child psychiatry diagnose autism and assign a diagnostic code, and all diagnoses are recorded in the Danish Psychiatric Central Register. We identified all children given a diagnosis of autistic disorder (ICD-10 code F84.0 and DSM-IV code 299.00) or another autistic-spectrum disorder (ICD-10 codes F84.1 through F84.9 and DSM-IV codes 299.10 and 299.80). When a child was given diagnoses of both autistic disorder and one or more other autistic-spectrum disorders, we classified the diagnosis as autistic disorder. Autism is associated with the inherited genetic conditions tuberous sclerosis, Angelman's syndrome, and the fragile X syndrome and with congenital rubella. To maximize the homogeneity of the study population, data for children with these conditions were censored when the diagnosis was made. We obtained information on these conditions from the National Hospital Registry.

We performed an extensive record review for 40 children with autistic disorder (13 percent of all the children with autistic disorder) to validate the diagnosis of autism. A consultant in child psychiatry with expertise in autism examined the medical records. Thirty-seven of the children (92 percent) met the operational criteria for autistic disorder according to a systematic coding scheme developed by the Centers for Disease Control and Prevention for surveillance of autism and used in a prevalence study in Brick Township, New Jersey.[27] The three children who did not meet the criteria for autistic disorder were all classified as having other autistic-spectrum disorders. For two of the children, the diagnosis of autistic disorder was questionable because of profound intellectual impairment. For the third child, we did not have information about the onset of symptoms before the age of three years, which is a prerequisite for the diagnosis of autistic disorder.

We obtained information on birth weight and gestational age from the Danish Medical Birth Registry and the National Hospital Registry.[28,29] Information on potential confounders, including socioeconomic status (as indicated by the employment status of the head of the household) and mother's education was obtained from Statistics Denmark from the time when the child was 15 months of age.

Statistical Analysis

Follow-up for the diagnosis of autistic disorder or another autistic-spectrum disorder began for all children on the day they reached one year of age and continued until the diagnosis of autism or an associated condition (the fragile X syndrome, Angelman's syndrome, tuberous sclerosis, or congenital rubella), emigration, death, or the end of follow-up, on December 31, 1999, whichever occurred first. The incidence-rate ratios for autistic disorder and other autistic-spectrum disorders in the group of vaccinated children, as compared with the unvaccinated group, were examined in a log-linear Poisson regression model with the use of PROC GENMOD (SAS, version 6.12).[30] We treated vaccination as a time-dependent covariate. The children were assigned to the nonvaccinated group until they received the MMR vaccine. From that date, they were followed in the vaccinated group. In additional analyses, the MMR-vaccinated children were grouped according to their age at the time of vaccination, the interval since vaccination, and the calendar period when vaccination was performed.

In reporting the results, we refer to the incidence-rate ratios as relative risks. For all risk estimates, we considered possible confounding by age (1, 2, 3, 4, 5, 6, 7, or 8 to 9 years), sex, calendar period (1992 to 1993, 1994, 1995, 1996, 1997, 1998, or 1999; for other autistic-spectrum disorders, the years 1992, 1993, and 1994 were grouped together), socioeconomic status (six groups), mother's education (five groups), gestational age (≤36, 37 to 41, or ≥42 weeks), and birth weight (≤2499, 2500 to 2999, 3000 to 3499, 3500 to 3999, or ≥4000 g).

RESULTS

A total of 537,303 children were included in the cohort and followed for a total of 2,129,864 person-years. Follow-up of 5811 children was stopped before December 31, 1999, because of a diagnosis of autistic disorder (in 316 children), other autistic-spectrum disorders (in 422), tuberous sclerosis (in 35), congenital rubella (in 2), or the fragile X or Angelman's syndrome (in 8), and because of death or emigration in the cases of 5028 children, whose data were censored. For children who received MMR vaccine, there were 1,647,504 person-years of follow-up, and for children who did not receive the vaccine, there were 482,360 person-years of follow-up.

Table 1 shows the distribution of the MMR cohort according to vaccination status, sex, birth weight, gestational age, socioeconomic status, mother's education, and age when autism was diagnosed. The mean age at diagnosis was four years and three months for autistic disorder and five years and three months for other autistic-spectrum disorders. The mean age at the time of the MMR vaccination was 17 months, and 98.5 percent of the vaccinated children were vaccinated before 3 years of age. The proportion of children who were vaccinated was the same among boys and girls (82.0 percent).

Table 2 shows the association between variables related to MMR vaccination and the risk of autism. We calculated the relative risk with adjustment for age, calendar period, sex, birth weight, gestational age, mother's education, and socioeconomic status. Overall, there was no increase in the risk of autistic disorder or other autistic-spectrum disorders among vaccinated

TABLE 1. CHARACTERISTICS OF THE 537,303 CHILDREN IN THE DANISH COHORT.

CHARACTERISTIC	VACCINATED CHILDREN (N=440,655)	UNVACCINATED CHILDREN (N=96,648)	P VALUE*
	number (percent)		
Sex			0.55
Male	226,042 (51.3)	49,680 (51.4)	
Female	214,613 (48.7)	46,968 (48.6)	
Birth weight			<0.001
≤2499 g	21,633 (4.9)	5,164 (5.3)	
2500–2999 g	53,874 (12.2)	12,062 (12.5)	
3000–3499 g	135,630 (30.8)	29,262 (30.3)	
3500–3999 g	135,255 (30.7)	29,143 (30.2)	
≥4000 g	66,358 (15.1)	14,563 (15.1)	
Data missing	27,905 (6.3)	6,454 (6.7)	
Gestational age			<0.001
≤36 wk	19,029 (4.3)	3,129 (3.2)	
37–41 wk	272,345 (61.8)	40,609 (42.0)	
≥42 wk	27,349 (6.2)	3,986 (4.1)	
Data missing†	121,932 (27.7)	48,924 (50.6)	
Socioeconomic status‡			<0.001
Manager (very high)	41,367 (9.4)	9,940 (10.3)	
Wage earner (high)	85,772 (19.5)	16,187 (16.7)	
Wage earner (medium)	70,906 (16.1)	13,753 (14.2)	
Wage earner (low)	116,503 (26.4)	26,699 (27.6)	
Wage earner (minimal)	57,408 (13.0)	10,996 (11.4)	
Unemployed	67,841 (15.4)	18,519 (19.2)	
Data missing	858 (0.2)	554 (0.6)	
Mother's education			<0.001
Postgraduate education	26,118 (5.9)	5,856 (6.1)	
College	67,776 (15.4)	14,599 (15.1)	
Vocational training	178,553 (40.5)	34,006 (35.2)	
Secondary school	42,667 (9.7)	10,164 (10.5)	
Primary school	114,768 (26.0)	28,680 (29.7)	
Data missing	10,773 (2.4)	3,343 (3.5)	
Age at diagnosis of autistic disorder			0.87
≤2 yr	48 (0.01)	9 (0.01)	
3–5 yr	187 (0.04)	31 (0.03)	
≥6 yr	34 (0.01)	7 (0.01)	
Age at diagnosis of another autistic-spectrum disorder			0.19
≤2 yr	32 (0.01)	3 (0.003)	
3–5 yr	202 (0.05)	37 (0.04)	
≥6 yr	118 (0.03)	30 (0.03)	

*P values are based on the chi-square test of statistical independence.

†Data were available from the Danish Medical Birth Registry only until December 31, 1996.

‡The employment status of the head of the household was used to indicate socioeconomic status.

Table 2. Adjusted Relative Risk of Autistic Disorder and of Other Autistic-Spectrum Disorders in Vaccinated and Unvaccinated Children.*

VACCINATION	PERSON-YEARS†	AUTISTIC DISORDER		OTHER AUTISTIC-SPECTRUM DISORDERS	
		NO. OF CASES	ADJUSTED RELATIVE RISK (95% CI)	NO. OF CASES	ADJUSTED RELATIVE RISK (95% CI)
Total	2,129,864	316		422	
Vaccination					
No	482,360	53	1.00	77	1.00
Yes	1,647,504	263	0.92 (0.68–1.24)	345	0.83 (0.65–1.07)
Age at vaccination					
Not vaccinated	482,360	53	1.00	77	1.00
≤14 mo	200,003	38	1.18 (0.78–1.80)	43	0.88 (0.60–1.28)
15–19 mo	1,320,753	195	0.86 (0.63–1.17)	270	0.83 (0.64–1.08)
20–24 mo	69,242	17	1.19 (0.69–2.07)	12	0.62 (0.33–1.13)
25–35 mo	40,935	11	1.20 (0.63–2.31)	15	1.09 (0.63–1.91)
≥36 mo	16,572	2	0.56 (0.14–2.30)	5	0.64 (0.26–1.59)
Interval since vaccination					
Not vaccinated	482,360	53	1.00	77	1.00
<6 mo	212,805	3	0.39 (0.11–1.32)	8	1.18 (0.51–2.75)
6–11 mo	197,931	21	1.38 (0.76–2.51)	4	0.31 (0.10–0.91)
12–17 mo	183,460	22	1.07 (0.59–1.95)	16	0.92 (0.47–1.80)
18–23 mo	168,045	31	0.86 (0.52–1.41)	16	0.47 (0.26–0.86)
24–29 mo	154,290	42	0.99 (0.61–1.58)	32	0.77 (0.46–1.27)
30–35 mo	139,258	33	0.86 (0.54–1.38)	27	0.69 (0.43–1.11)
36–59 mo	406,320	90	0.99 (0.66–1.50)	158	1.05 (0.77–1.45)
≥60 mo	185,396	21	0.67 (0.34–1.33)	84	0.75 (0.51–1.09)
Date of vaccination					
Not vaccinated	482,360	53	1.00	77	1.00
1991–1992	248,646	31	1.00 (0.59–1.70)	61	0.75 (0.51–1.09)
1993–1994	659,152	81	0.73 (0.50–1.06)	146	0.74 (0.56–0.99)
1995–1996	475,990	96	0.91 (0.63–1.30)	116	1.13 (0.81–1.56)
1997–1999	263,716	55	1.35 (0.84–2.17)	22	0.71 (0.40–1.24)

*The relative risk was adjusted for age, calendar period, sex, birth weight, gestational age, mother's education, and socioeconomic status of the family. The reference group was the group of children who were not vaccinated. The distribution of cases of autistic disorder or other autistic-spectrum disorders according to vaccination status differs from that in Table 1 because, in this analysis, children who were vaccinated after the disorder had been diagnosed were classified according to their vaccination status at the time of the diagnosis (i.e., as unvaccinated). CI denotes confidence interval.

†Because of rounding, the numbers of person-years do not necessarily sum to the total shown.

children as compared with unvaccinated children (adjusted relative risk of autistic disorder, 0.92; 95 percent confidence interval, 0.68 to 1.24; adjusted relative risk of other autistic-spectrum disorders, 0.83; 95 percent confidence interval, 0.65 to 1.07). Furthermore, we found no association between the development of autistic disorder and the age at vaccination (P=0.23), the interval since vaccination (P=0.42), or the calendar period at the time of vaccination (P=0.06).

Adjustment for potential confounders with the exception of age resulted in similar estimates of risk. Changing the start of follow-up for autistic disorder and other autistic-spectrum disorders to the date of birth or 16 months of age had little effect on the estimates (data not shown). Furthermore, including children with the fragile X syndrome, tuberous sclerosis, congenital rubella, or Angelman's syndrome in the analysis did not change the estimates (data not shown).

DISCUSSION

This study provides three strong arguments against a causal relation between MMR vaccination and autism. First, the risk of autism was similar in vaccinated and unvaccinated children, in both age-adjusted and fully adjusted analyses. Second, there was no temporal clustering of cases of autism at any time after immunization. Third, neither autistic disorder nor other autistic-spectrum disorders were associated with MMR vaccination. Furthermore, the results were derived from a nationwide cohort study with nearly complete follow-up data.

All previous studies of an association between autism and MMR vaccination have been case series,[1,14,15] ecologic studies,[11,12] or cross-sectional studies,[10,13] and the majority have not used optimal data for risk assessment. In a well-conducted, cross-sectional prevalence study, Taylor and colleagues[10] found that there was no sharp increase in the prevalence of autism after the introduction of the MMR vaccine. However, it could be argued that a more gradual increase would be expected, since autism is characterized by an insidious onset and a delay in diagnosis. A case-series study by Peltola et al.[15] also provides evidence against a causal connection.

One of the main reasons for public concern has been that the widespread use of the MMR vaccine in some regions appeared to coincide with an increase in the incidence of autism. However, this is not a uniform finding. In Denmark, the prevalence of autism (according to the criteria of the *International Classification of Diseases, 8th Revision*) was less than 2.0 cases per 10,000 children between the ages of five and nine years in the 1980s and the beginning of the 1990s. Since then, the rates have increased in all age groups except for children younger than two years of age, and in 2000, the prevalence of autism (according to the ICD-10 criteria) was higher than 10.0 cases per 10,000 children five to nine years of age (unpublished data). Thus, the increase in autism both in California[5] and in Denmark occurred well after the introduction of the MMR vaccine.

Our study was based on individual reports of vaccination and diagnoses of autism in a well-defined geographic area. The exposure data were collected prospectively, independently of parental recall and before the diagnosis of autism. Furthermore, the diagnosis was recorded independently of the recording of MMR vaccination. Thus, there was little possibility of differential misclassification of exposure or outcome measures. Furthermore, our analysis was based on complete follow-up data.

We assume that the data on MMR vaccination are almost complete, since general practitioners in Denmark are reimbursed only after reporting immunization data to the National Board of Health. We had an unvaccinated reference group with almost 500,000 person-years of follow-up, even though the study was numerically imbalanced in favor of the vaccinated group. The power of the study is reflected in the narrow 95 percent confidence intervals.

We had no information on the presence or absence of a family history of autism, which could explain our negative findings only if families with a history of autism avoided MMR vaccination. If so, we would expect to have found high relative risks at the beginning of the study period, before the hypothetical link between vaccination and autism was publicized. This was not the case. We had no information on whether the children with autism had regression, and thus we could not perform a subgroup analysis. However, the fact that the overall relative risk of autism or an autistic-spectrum disorder was less than 1.0 does not support the possibility of a subgroup of vulnerable children.

The Danish vaccination program recommends that children receive the MMR vaccine at 15 months of age and provides the vaccination free of charge. Among the children in our cohort who were born in 1995, the rate of MMR vaccination was lower than the rate of vaccination with the first *Haemophilus influenzae* type B vaccine (86.9 percent vs. 97.0 percent). However, the rate of MMR vaccination in our study was similar to that in the United States (87.6 percent in 1995) and Belgium (83.0 percent in 1997).[31,32] Nevertheless, the main concern is the comparability of vaccinated and nonvaccinated children in relation to the end point under study. In all analyses, when risk estimates were calculated, we controlled for possible confounders (age, sex, calendar period, socioeconomic status, mother's education, gestational age, and birth weight). Except for age, none of these possible confounders changed the estimates. The confounding by age was a function of the time available for follow-up, since much of the follow-up for the unvaccinated group involved young children, in whom autism is often undiagnosed.

We assessed the validity of the diagnosis of autistic disorder in a subgroup of children and found it to be high. This was to be expected, since only specialists in child and adolescent psychiatry are authorized to code the diagnosis of autism in the Danish Psychiatric Central Register. All schools have access to health care personnel as well as psychologists. Because of the comprehensive health care surveillance for children in Denmark, all severe cases of autism are likely to be diagnosed and reported to the registry at some point. Reporting of the other autistic-spectrum disorders is less complete than that for autistic disorder, and some diagnoses are almost certainly missed. However, it is unlikely that this misclassification would be associated with vaccination status. It is very difficult to determine the onset of autism, and many cases are probably due to prenatal factors. Our records did not contain information on when the first autistic symptoms were noted, and we could not adjust for a differential delay in the diagnosis. Again, it is highly unlikely that a delayed diagnosis was associated with MMR vaccination in this study.

There are few published data on the incidence of autism, but the prevalence rates reported in the literature vary widely, from 1.2 cases per 10,000 (according to the criteria of the third edition of the *Diagnostic and Statistical Manual of Mental Disorders*) to 30.8 per 10,000 (according to the ICD-10 criteria).[33,34] The prevalence rates among eight-year-old children in our cohort were 7.7 per 10,000 for autistic disorder and 22.2 per 10,000 for other autistic-spectrum disorders. These rates are similar to the prevalence rates of 5.4 per 10,000 for autistic disorder and 16.3 per 10,000 for other autistic-spectrum disorders in a cohort of 325,347 French children (ICD-10 criteria), reported by Fombonne et al.,[35] and the rate of 11 per 10,000 for autistic disorder in a cohort of U.S. children (DSM-IV criteria), reported by Croen and colleagues.[36] The DSM-IV classification system used in the United States and the ICD-10 classification system used in many European countries are almost identical with regard to the classification of autistic disorder.[23-26] In our validity substudy, we found that 93 percent of cases diagnosed according to the ICD-10 criteria met the DSM-IV operational criteria for the diagnosis of autistic disorder.

Supported by grants from the Danish National Research Foundation; the National Vaccine Program Office and National Immunization Program, Centers for Disease Control and Prevention; and the National Alliance for Autism Research.

We are indebted to Susanne Toft and Meta Jørgensen for the abstraction and review of medical records and to Catherine Rice and Nancy Dornberg for assistance with the validity substudy.

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This Week in the Journal

November 7, 2002

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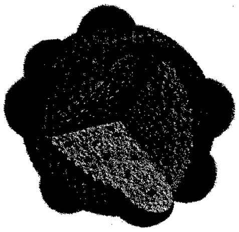
This national cohort study, which included 537,303 children, obviated the problems of selection bias and misclassification bias. The results provide strong evidence that MMR vaccination is not a cause of autism.

see page 1477 (Perspective, page 1474)



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see page 1483 (editorial, page 1522)

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PERSPECTIVE

Suspicions about the Safety of Vaccines

Vaccines represent one of the most effective interventions in medicine. They can protect whole populations from potentially dangerous diseases. Because vaccines are usually given to healthy people, especially children, any concern about the safety of vaccines has to be taken very seriously. Even with close scrutiny, the overall safety record of vaccines is extraordinarily good.

Examples of Unsubstantiated Claims Made about Some Vaccines.

VACCINE	UNSUBSTANTIATED ADVERSE EFFECTS
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***Haemophilus influenzae* type b**	Diabetes mellitus
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Lyme disease vaccine	Chronic inflammatory arthritis
"Hot lots" (some batches of any vaccine)	Multiple systemic problems
Multiple vaccinations	Undefined harmful immunologic effects from vaccine interactions

Despite this safety record, for a surprising number of vaccines, there have been widely publicized but unsubstantiated claims of adverse effects (see Table). When suspicions about a vaccine begin to spread, there may be dangerous consequences for the public health. Such is currently the case with the live attenuated measles virus in the vaccine against measles, mumps, and rubella (MMR), which some people erroneously believe is a cause of autism.

Vaccines can cause serious adverse reactions. Documented examples include paralytic disease from the live polio vaccine and intestinal obstruction from the rotavirus vaccine. When these problems occurred, they were recognized and addressed. Because of fears of bioterrorism and smallpox, it is possible that vaccinia vaccination may resume. The live-virus vaccinia vaccine causes many adverse reactions, including rare but severe, or even fatal, infectious complications.

Concern about autism and the measles component of the MMR vaccine began with the awareness that encephalitis is a rare but devastating complication of measles. Some survivors of measles have immune-mediated postinfectious encephalomyelitis with seizures and mental retardation. The hypothesis about the measles vaccine and autism also rests in part on some widely publicized research involving a small number of young children with chronic gastrointestinal symptoms and behavioral abnormalities. The researchers speculated on a causal relation among MMR vaccination, abnormalities in lymphoid tissue, and developmental disorders such as autism. Together, these findings have led some to conclude that the measles virus in the MMR vaccine is a cause of autism in children.

When a child has autism, the parents begin to notice problems during the second and third years of life. Sometimes, there is severe regression in language and social skills in young children who initially seemed to be developing quite normally. Since the MMR vaccine is given at the beginning of the second year of life, there is a temporal association between vaccination and the recognition of autism. The situation is further complicated because the frequency of autism appears to have increased by at least a factor of five during the past 20 years. This increase is probably the result of better reporting and wider use of this diagnosis to describe children with unexplained cognitive and behavioral disorders. However, fears only grow when there appears to be an increase in the prevalence of a severe and unexplained disease in children.

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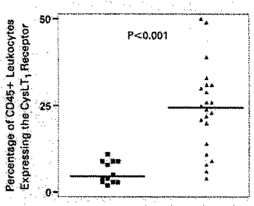
Unfortunately, objective data are not likely to put an end to the controversy. Strongly held beliefs are difficult to change. We live in an era in which the public does not have a high degree of trust in the vaccine manufacturers, the government, or the medical establishment. Consumers have become highly sensitive about safety, and their confidence has not been bolstered by



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Patients who are hypersensitive to aspirin have asthma, rhinosinusitis, and nasal polyposis. These findings have been attributed in part to the action of the cysteinyl leukotrienes at one of their receptors. Although aspirin can initiate the reaction, it can also be an effective treatment, since long-term exposure to aspirin leads to a desensitized state. In this study, the authors show that patients with aspirin-sensitive rhinosinusitis have enhanced expression of the cysteinyl leukotriene receptor CysLT$_1$ on inflammatory cells in nasal-biopsy specimens and that desensitization with aspirin is associated with decreased expression of this receptor on these cells.

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see page 1493 (editorial, page 1524)

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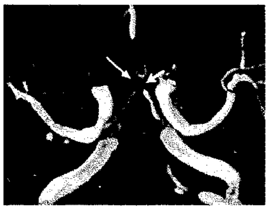
Unsubstantiated accusations that a vaccine causes harm can have serious consequences. Some people begin to avoid vaccination, increasing the number at risk, particularly in communities where anti-vaccine activists are most successful. Once a vaccine has been tied repeatedly to even an unsupported claim of an adverse effect, costly legal action usually follows, even if the vaccine is eventually proved to be safe. The companies that produce vaccines come to associate vaccines with adverse economic effects for themselves, with little profit and huge liability. Effective vaccines may be withdrawn from the market. It becomes harder to run vaccination programs, including those in developing countries where the needs are greatest.

Those arguing against vaccination forget how bad the illnesses and their complications can be. They forget that in this country before the development of the measles vaccine, thousands of children had severe illness from measles, sometimes resulting in permanent disability. In 1960, 400 children died from measles. But the biggest tragedy is that outside of the developed countries, more than a million children still die from this disease each year. Those deaths are preventable by a measles vaccine that is cost effective and safe. Children everywhere deserve the protection that carefully developed, carefully monitored vaccines can provide against so much disease.

EDWARD W. CAMPION, M.D.



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see page 1500

> ***"An estimated 19.2 million adults in the United States have stage 1, 2, 3, or 4 kidney disease."***

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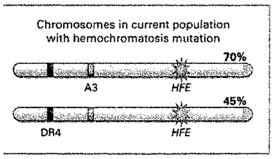
see page 1505


Chromosomes in current population with hemochromatosis mutation
70%
A3
HFE
45%
DR4
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Genomic Medicine: **Genomic Medicine — A Primer**

This review article launches our series on genomic medicine. It provides definitions of terms commonly used in genetics, delineates the distinction between genetics and genomics, and supplies examples of the ways in which genetic information can be used in the day-to-day care of patients. The mechanisms leading to the availability of more than 100,000 proteins from only approximately 30,000 genes are described. The various common types of mutations are identified and defined, and modes of inheritance — from simple mendelian to complex to mitochondrial — are detailed.

see page 1512 (editorial, page 1526)

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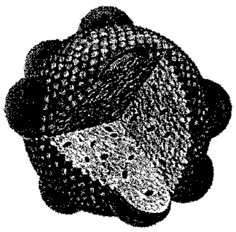

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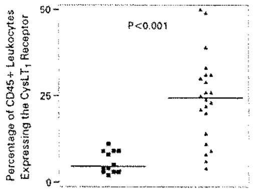

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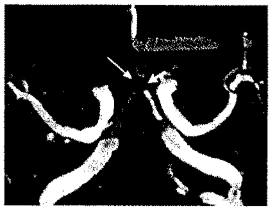

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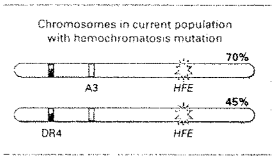
This article reviews the classification of nondiabetic kidney disease and approaches to slowing disease progression.

see page 1505


Chromosomes in current population with hemochromatosis mutation
70%
A3
HFE
45%
DR4
HFE

Genomic Medicine: **Genomic Medicine — A Primer**

This review article launches our series on genomic medicine. It provides definitions of terms commonly used in genetics, delineates the distinction between genetics and genomics, and supplies examples of the ways in which genetic information can be used in the day-to-day care of patients. The mechanisms leading to the availability of more than 100,000 proteins from only approximately 30,000 genes are described. The various common types of mutations are identified and defined, and modes of inheritance — from simple mendelian to complex to mitochondrial — are detailed.

see page 1512 (editorial, page 1526)

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Congress of the United States

House of Representatives

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BERNARD SANDERS, VERMONT,
INDEPENDENT

November 21, 2002

The President
The White House
Washington, D.C. 20500

Dear Mr. President:

I am writing to urge you to host a White House conference on autism to galvanize a national effort to determine why autism has reached epidemic proportions in this country.

Fifteen years ago, one in 10,000 children in the United States was autistic. Today, estimates place that number at one in 250. A recent study funded by the State of California determined that the number of autistic children in California has tripled, and that the increase could not be attributed to better diagnoses or more accurate testing.

This explosive growth in autism has had devastating consequences for families and communities all across the country. Families of autistic children face great emotional and financial hardships as they seek to care for their children. Local school districts have been overwhelmed financially and logistically as they attempt to educate these children with so many special needs. As a nation, we must develop solutions to help families and communities cope with these challenges.

We must also try to determine what is causing this outbreak and how it can be stopped. One possible explanation is the mercury preservative that was used for years in pediatric vaccines. It is troubling that at the same time that autism was skyrocketing, additional vaccines were being added to the routine vaccination schedule, increasing the cumulative amount of mercury to which young children were exposed. The Institute of Medicine called this theory unproven, but "biologically plausible," and called for much more research. Other factors may also be behind this increase, and it is entirely possible that a combination of factors in the environment may be at work.

The President
November 21, 2002
Page 2

At a White House conference, you could bring together the best minds from across the country to chart a course of scientific research to uncover the underlying causes of this epidemic Right now such research is not being aggressively pursued. You could also bring together parents of autistic children and leaders in the fields of education and social services to begin to address the difficult challenges they face.

Mr. President, you are in a unique position to provide the leadership that is necessary to organize a national effort to resolve these problems. Members of the House and Senate would, without a doubt, work with you to mobilize whatever resources are necessary to mount such an effort. I urge you to host a White House conference on autism.

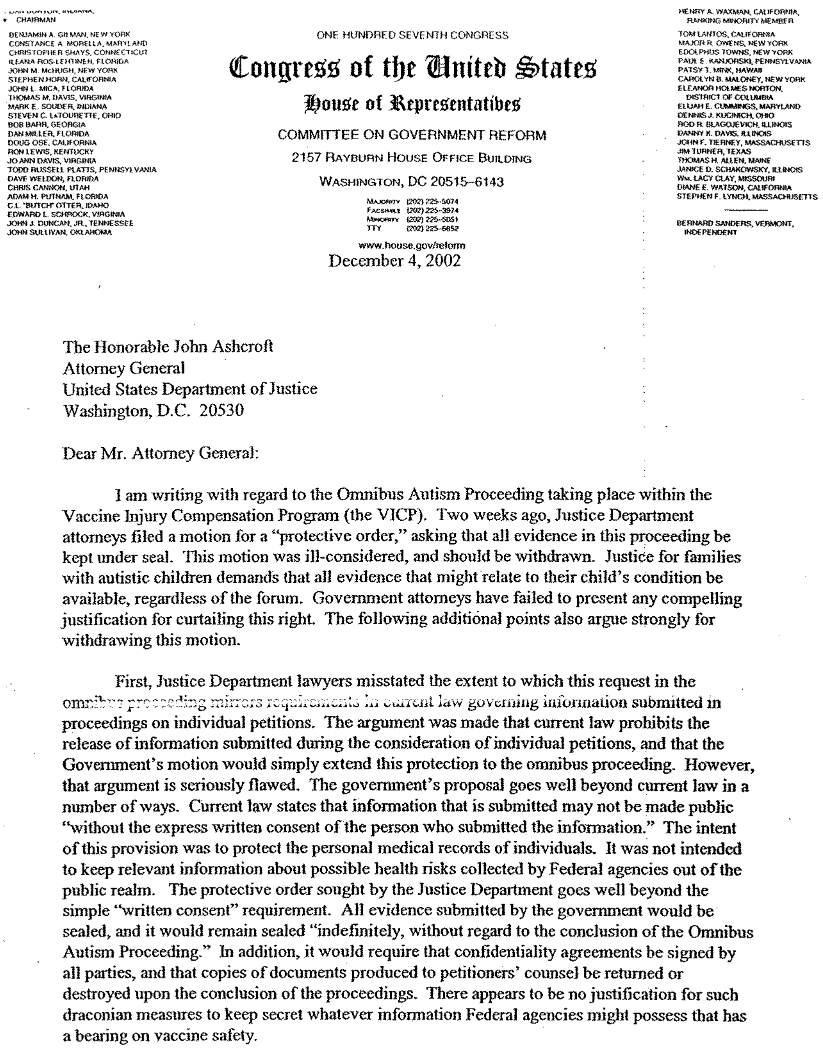
Thank you very much for your leadership, and for your consideration of this request.

Sincerely,

Dan Burton
Chairman

cc: The Honorable J. Dennis Hastert
Speaker of the House

The Honorable Trent Lott
Majority Leader-Elect
United States Senate



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BERNARD SANDERS, VERMONT,
INDEPENDENT

December 4, 2002

The Honorable John Ashcroft
Attorney General
United States Department of Justice
Washington, D.C. 20530

Dear Mr. Attorney General:

I am writing with regard to the Omnibus Autism Proceeding taking place within the Vaccine Injury Compensation Program (the VICP). Two weeks ago, Justice Department attorneys filed a motion for a "protective order," asking that all evidence in this proceeding be kept under seal. This motion was ill-considered, and should be withdrawn. Justice for families with autistic children demands that all evidence that might relate to their child's condition be available, regardless of the forum. Government attorneys have failed to present any compelling justification for curtailing this right. The following additional points also argue strongly for withdrawing this motion.

First, Justice Department lawyers misstated the extent to which this request in the omnibus proceeding mirrors requirements in current law governing information submitted in proceedings on individual petitions. The argument was made that current law prohibits the release of information submitted during the consideration of individual petitions, and that the Government's motion would simply extend this protection to the omnibus proceeding. However, that argument is seriously flawed. The government's proposal goes well beyond current law in a number of ways. Current law states that information that is submitted may not be made public "without the express written consent of the person who submitted the information." The intent of this provision was to protect the personal medical records of individuals. It was not intended to keep relevant information about possible health risks collected by Federal agencies out of the public realm. The protective order sought by the Justice Department goes well beyond the simple "written consent" requirement. All evidence submitted by the government would be sealed, and it would remain sealed "indefinitely, without regard to the conclusion of the Omnibus Autism Proceeding." In addition, it would require that confidentiality agreements be signed by all parties, and that copies of documents produced to petitioners' counsel be returned or destroyed upon the conclusion of the proceedings. There appears to be no justification for such draconian measures to keep secret whatever information Federal agencies might possess that has a bearing on vaccine safety.

Second, this "protective order" would place attorneys representing families of autistic children in an untenable ethical position. In some cases, families may reject the judgement reached in the VICP and opt to file a lawsuit. If the family's attorney is aware of information developed in the VICP that would strengthen the family's case in court, he would be constrained from using it, denying the family effective representation. Furthermore, an attorney in this awkward position may feel compelled to recommend to his clients that they accept a decision in the VICP that he does not feel would be in their best interest, knowing that important evidence may not be available for use in a later lawsuit.

Finally, this motion provides ammunition to critics of government vaccine policy who believe that Federal policymakers side too frequently with the interests of vaccine manufacturers. It creates the appearance, fairly or unfairly, that this protective order is meant to protect pharmaceutical companies at the expense of families with autistic children. We have an epidemic on our hands. Fifteen years ago, one in 10,000 American children was autistic. Today, the number is one in 250. This is not the time for legal jousting over arcane rules of evidence. All of our efforts should be geared toward uncovering the causes of this epidemic, reversing this trend, and giving as much information as possible to the public.

The interest of the Federal government should not be to protect any particular party in this matter. The interest of the Federal government should be to find the truth and lay it out for all to see. I urge you to instruct the appropriate officials to withdraw this motion and allow this proceeding to move forward unencumbered.

Thank you very much for your consideration.

Sincerely,

Dan Burton
Chairman

cc: The Honorable George Hastings
Special Master
Court of Federal Claims

The Honorable Henry Waxman
Ranking Minority Member

[redacted]

[redacted]

Sent: Tuesday, December 17, 2002 9:42 AM

[redacted]

Subject: FW:

[redacted]

Attached is one of the two articles Mr. Souder would like included in the record on last week's vaccination hearing.

Thanks for your help.

[redacted]

-----Original Message-----
From:
Sent: None
Subject:

1. This is the statement Lilly will issue today at Mr. Burton's hearing. It gives you some background on the issue.

2. We would like to see the following editorial

included in the hearing record.

THE WALL STREET JOURNAL

REVIEW & OUTLOOK (Editorial)
The Truth About Thimerosal
968 words
5 December 2002
The Wall Street Journal
A18
English
(Copyright (c) 2002, Dow Jones & Company, Inc.)

Was it nefarious Dick Armey? Dastardly Senator and Dr. Bill Frist? Or maybe a phantom pediatrician, hired by Eli Lilly to haunt the halls of Congress? From the press coverage, you'd think there's no greater question than who put the now-famous thimerosal rider into the Homeland Security Bill.

Washington has been so busy playing political "Where's Waldo?" that no one has actually bothered to explain the merits. We're happy to fill this void with the facts, especially because they show that protecting thimerosal from runaway legal liability is the right thing to do as a matter of public health. Far from ducking behind Capitol pillars, Republicans should be trumpeting their support.

The story of thimerosal begins in the 1930s, when it was introduced into vaccines to prevent infections from fungus and bacteria. The preservative, an organic mercury compound, was so safe and uncontroversial that nobody even noticed it for 60 years.

Then in 1997, as part of the FDA Modernization Act, Congress required the agency to do an inventory of mercury in all of its licensed drugs and vaccines. By 1999, researchers realized that kids were getting more shots these days, and that the thimerosal combined from all the vaccinations could, theoretically, slightly exceed an EPA mercury guideline. The findings were manna to the small but vocal anti-vaccination lobby that has spent years falsely claiming vaccines cause everything from multiple sclerosis to cancer. They soon claimed that thimerosal caused autism.

In retrospect, the researchers we've talked to agree it was the EPA standard that was the problem. The agency had based its number on a study of pregnant women whose ingestion of significant and sustained amounts of methyl mercury had led to children who later scored slightly lower on neurological and cognitive tests (nothing near autism). The EPA estimated the lowest possible amount a mother could have ingested to be associated with a disorder and then, to be ridiculously safe, divided that by 10. The agency's standard is below that of even the hyper-cautious Food and Drug Administration.

There's little evidence vaccines exceed even that extremely low level. Just last week a University of Rochester study published in Lancet looked at 61 infants -- 40 receiving vaccines containing thimerosal, and 21 receiving thimerosal-free vaccines. Most children had blood mercury levels of 1 or 2 nanograms per milliliter; the highest level, found in one child, was 4.11 ng/ml.

By comparison, the EPA standard is 5.9 ng/ml. The study also found that children excrete ethyl mercury more quickly than expected, so that it doesn't build up from one vaccination to the next. "A mom who eats a tuna fish sandwich probably passes along more mercury during breast-feeding than a kid gets in a vaccination," says Michael Pichichero, the study's lead investigator.

Most important, no scientific study has ever found a link between vaccines and autism, despite years of detailed research into the safety of vaccines. Even the World Health Organization continues to endorse the use of the preservative.

Sadly, the real losers of this wild goose chase are parents of autistic children, who've seen anti-vaccinators use their cause to divert time and resources away from legitimate research into the disorder.

U.S. public health agencies knew most of this in 1999. But they worried that anti-vaccine groups would use the FDA information to scare parents away from immunizations. So they hastily recommended that manufacturers immediately remove the preservative -- a huge mistake.

"We took it out precipitously, which made it look like thimerosal is harmful -- when there is no evidence it is. I think we hurt the public trust," said Paul Offit, who sits on the Advisory Committee on Immunization Practices and is chief of infectious diseases at the Children's Hospital of Philadelphia.

The recommendation brought unwarranted fear, vaccine shortages, and . . . tort lawyers. Usually, parents of the rare child injured by a vaccine must go through the Vaccine Injury Compensation Program before they can sue in regular courts. Set up by Congress in 1986 after lawsuits all but bankrupted vaccine makers, VICP ensures that victims get compensated quickly for genuine wrongs.

But the tort lawyers hate that VICP cuts out their giant fees, and they saw an opening in thimerosal. They've exploited every loophole to keep frivolous thimerosal cases out of VICP, and have instead filed hundreds of lawsuits against vaccine makers and Eli Lilly (which stopped making thimerosal 10 years ago). The four vaccine makers left are today stuck devoting their funds not to research into new, life-saving vaccines, but to paying legal bills.

These, readers, are the facts behind the thimerosal rider that is supposed to be so scandalous. All the legislation does is require that parents first go through VICP, as with any vaccine claim. They can sue later in other courts, if they choose (and assuming a statute of limitations problem is fixed). The vaccine court is much better positioned than other courts to decide on the merits of thimerosal cases. And it has the added social benefit of protecting vaccine research and production at a time when we need both to defend against bioterror.

None of this makes trial lawyers rich, though, and so they asked Senate Democrats, led by Joe Lieberman, to strip the rider away. They lost, but they did such a good media job that new Majority Leader Trent Lott has promised modifications to protect nervous Republicans who clearly haven't bothered to understand the issue.

We suggest they talk to Dr. Frist, who could supply a nerve transplant. If Republicans can't explain to parents that thimerosal is about supplying safe vaccines to their children, they don't deserve the majority.

3. The following documents were supplied by J. Craig Burton, Health Policy Advisor, Senator Bill Frist, M.D. (202-224-7139). Sen. Frist's press release and the ACCV statement, are also documents that we would like in the hearing record.

(If you are unable to open up this wpd document, I've included the text version of Senator Frist's press release below.)

Advisory Commission On Childhood Vaccines Urges Passage Of Comprehensive Vaccine Bill
Letter Supports Frist's Efforts to Balance Vaccine Program, Reduce Shortages

Monday, December 9, 2002
Press Release Of Senator Bill Frist, M.D.

WASHINGTON, D.C. – U.S. Senator Bill Frist (R-TN) today hailed the Advisory Commission on Childhood Vaccines' (ACCV) support of vaccine provisions included in the Homeland Security bill. A letter to Health and Human Services (HHS) Secretary Tommy Thompson from ACCV included support for the vaccine provisions in the homeland security bill and urged immediate action on Frist's comprehensive legislative vaccine package. ACCV is a nonpartisan panel made up of health professionals, lawyers and individuals that advise Secretary Thompson on improving the Vaccine Injury Compensation Program.

"Much focus has been placed on the vaccine provisions in the Homeland Security bill, which are only part of a larger, more comprehensive legislative package aimed at restoring balance to the vaccine program," said Frist. "Vaccine shortages threaten our children and the health of our nation, yet unnecessary litigation continues to destabilize our vaccine supply by causing fewer vaccines to be developed and produced. Today's nonpartisan expert recommendations highlight the importance of the provisions we have already passed and the critical need to press forward and make remaining changes to stabilize our nation's vaccine supply. This legislation is critical to protecting our children and nation, and I'm pleased to receive ACCV's support."

Frist's "Improved Vaccine Affordability and Availability Act" would improve the existing Vaccine Injury Compensation Program by providing additional compensation and protections for those who experience rare, but serious, side effects from vaccines and by stabilizing the vaccine supply and production market. Just one of the pending lawsuits in the United States seeks $30 billion in damages, while the total global value of the vaccine market is only $5 billion.

A Government Accounting Office (GAO) report released in September identified liability concerns and costs as one of several factors leading to vaccine shortages, and the need to improve our vaccine stockpiles to cushion future shortages. The report , "Childhood Vaccines: Ensuring an Adequate Supply Poses Continuing Challenges," also noted that the potential for reoccurrences of shortages exists.

Frist is the ranking member of the Public Health Subcommittee. He cosponsored the legislation with Senators Kay Bailey Hutchison (R-TX), Zell Miller (D-GA), Jim Bunning (R-KY) and Jim Jeffords (I-VT) in March of this year.

Please give me a call if you need further clarification or have any questions.

Call me on my cell phone if I don't answer at the office. (301)-685-7091

Thanks,

Suzanne

~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
Suzanne K. Simala
Senior Federal Relations Associate

Eli Lilly and Company
Government Relations
555 Twelfth Street, NW, Suite 650
Washington, DC 20004
ph 202-434-1029
fax 202-393-7960
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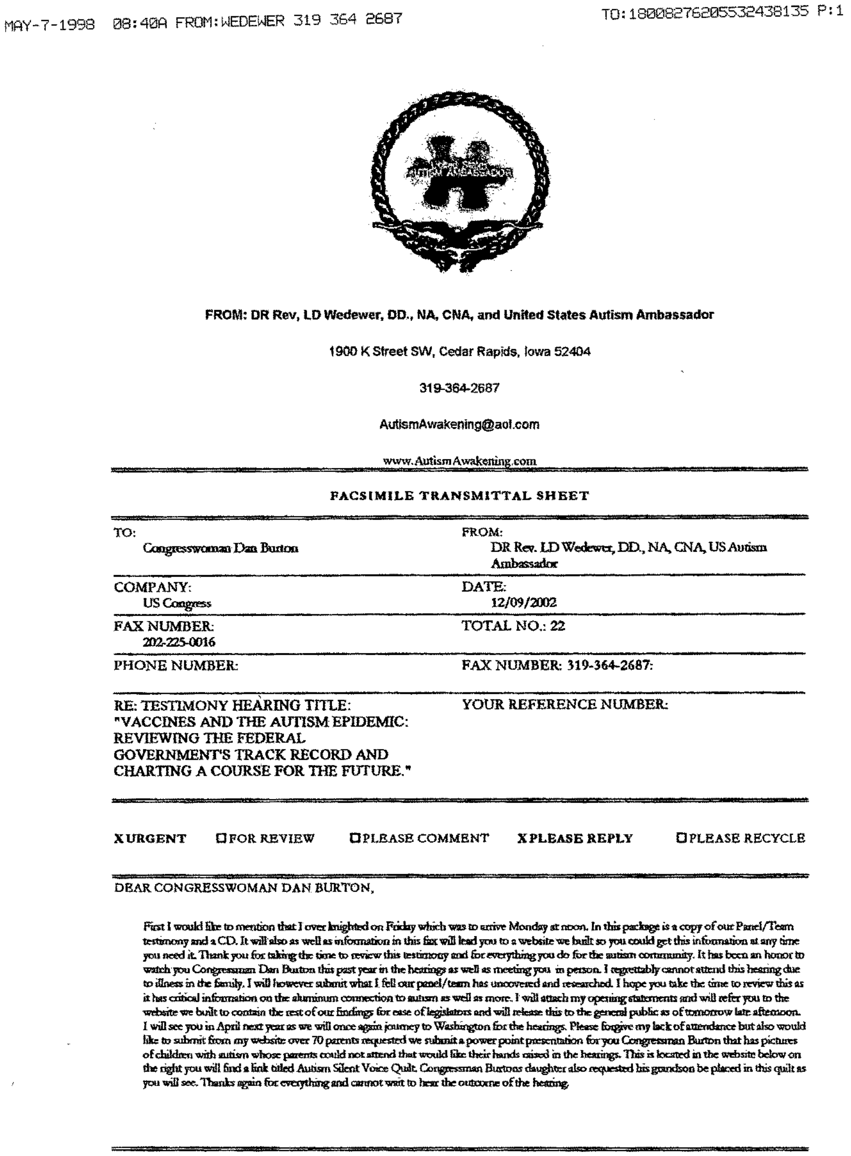

MAY-7-1998 08:40A FROM:WEDEWER 319 364 2687 TO:18008276205532438135 P:1

FROM: DR Rev, LD Wedewer, DD., NA, CNA, and United States Autism Ambassador

1900 K Street SW, Cedar Rapids, Iowa 52404

319-364-2687

AutismAwakening@aol.com

www.AutismAwakening.com

FACSIMILE TRANSMITTAL SHEET

TO: Congresswoman Dan Burton	FROM: DR Rev. LD Wedewer, DD., NA, CNA, US Autism Ambassador
COMPANY: US Congress	DATE: 12/09/2002
FAX NUMBER: 202-225-0016	TOTAL NO.: 22
PHONE NUMBER:	FAX NUMBER: 319-364-2687:
RE: TESTIMONY HEARING TITLE: "VACCINES AND THE AUTISM EPIDEMIC: REVIEWING THE FEDERAL GOVERNMENT'S TRACK RECORD AND CHARTING A COURSE FOR THE FUTURE."	YOUR REFERENCE NUMBER:

X URGENT ☐ FOR REVIEW ☐ PLEASE COMMENT X PLEASE REPLY ☐ PLEASE RECYCLE

DEAR CONGRESSWOMAN DAN BURTON,

First I would like to mention that I over knighted on Friday which was to arrive Monday at noon. In this package is a copy of our Panel/Team testimony and a CD. It will also as well as information in this fax will lead you to a website we built so you could get this information at any time you need it. Thank you for taking the time to review this testimony and for everything you do for the autism community. It has been an honor to watch you Congressman Dan Burton this past year in the hearings as well as meeting you in person. I regrettably cannot attend this hearing due to illness in the family. I will however submit what I fell our panel/team has uncovered and researched. I hope you take the time to review this as it has critical information on the aluminum connection to autism as well as more. I will attach my opening statements and will refer you to the website we built to contain the rest of our findings for ease of legislators and will release this to the general public as of tomorrow late afternoon. I will see you in April next year as we will once again journey to Washington for the hearings. Please forgive my lack of attendance but also would like to submit from my website over 70 parents requested we submit a power point presentation for you Congressman Burton that has pictures of children with autism whose parents could not attend that would like their hands raised in the hearings. This is located in the website below on the right you will find a link titled Autism Silent Voice Quilt. Congressman Burtons daughter also requested his grandson be placed in this quilt as you will see. Thanks again for everything and cannot wait to hear the outcome of the hearing.

Please contact me with any questions at: 319-431-8993 319-354-2687 (FAX/Phone) or Email: USAutismAmbassadr@aol.com

We really appreciate the work that all of the Autism Ambassadors have done and would like to see this proclamation signed in their honor. Thanks again for your help in this matter.

Peacefully,
LD Wedewer
1900 K Street SW
Cedar Rapids, Iowa 52404-3620

LD WEDEWER, US AUTISM AMBASSADOR

TESTIMONY FOR DECEMBER 10, 2002 GOVERMENT REFORM HEARING TITLED

"Vaccines and the Autism Epidemic: Reviewing the Federal Government's Track Record and Charting a Course for the Future."

Congressman, Christopher Shays, Congressman Dave Weldon,
Congressman Dan Burton the Honorable Chairman, and distinguished committee members,

Thank you for allowing me to enter my testimony into congressional record. First let me begin by saying thank-you for everything that Congressman Dan Burton and this committee has done to help those with autism and their families. I would like to disclose that I am not anti-vaccine but want to ensure safe vaccines and policies. I want to alert the Chairman and committee that my testimony was sent over-night on Friday to Congressman Dan Burton's Office. It will arrive Monday by 12:00 in a white box with writing all over it. It contains a book and CD set.

The Contents of this opening statement, the contents of this notebook, and CD is my testimony and the many individual's testimonies, and research into Autism and vaccines comparison, causes and effects. These individuals worked many sleepless nights and worked very hard to make sure the information gathered we believed to be accurate. It is our belief that once you see the names you will know how creditable the material is.

The title of the Book and CD requested to also be entered into testimony is: Vaccine Summary Comparison Reports and Charts©: Autism, Alzheimer's, Aluminum, Mercury, Arsenic, Copper, Lead, Thallium, Iron, and Formaldehyde.

In older studies we found that it was once believed that aluminum was not so toxic. In our studies we found that this is not quite the case. In our studies and chart we show how aluminum mirrors mercury and more then ten folds the effect of mercury. We will explain many other metals and how they compare. I want you to understand that with aluminum mirroring mercury if we take mercury out, would not the aluminum still do the same thing? This is what we wanted to find out and why we began this research and studies. I will refer you to this chart in the Book and CD: Summary Comparison of Characteristics of Autism, Aluminum, & Mercury Poisoning© In this chart we illustrate what we found in common between the three, they go across the chart for, Autism, Mercury, and ALUMINUM. SO for instance one cause's brain damage, they all across the charts were found to have the same problem.

We also found this of Arsenic and Iron in separate charts in the book. You can look across the chart with autism almost line for line. This is scary folks that in essence now means that Thimerosal, Aluminum, Arsenic, and Autism all mirror. I wish I could say that it stopped there but when Jan Brohart worked on Alzheimer's in collaboration with our team we found that autism also mirrored Alzheimer's. I personally have been working on Iron theories on Iron for a few years about the same year Kathy Blanco began hers. Our surveys were much the same so we have shared information on these findings and I must say that Iron also plays a large role in autism.
In our findings with this we also noted that we were running into Alzheimer's and many other mirror type illnesses which we explain in these reports.

With the help of all the individuals involved in these studies we were able to also find over 25 illnesses that also seem to mirror many to all of the same effects from aluminum and mercury.

We also found more conflicts of interest you will also find those in the book and CD.

These issues listed above and in the outlines book and CD you will see why this information was so critical to get to you before the hearing as the team and I, may not be able to attend the hearing, but would like to submit the information requested and this opening letter as testimony in the December 10, 2002 Autism Hearing.

We felt compelled due to the nature of our findings to hurry and put this together for the Honorable Dan Burton as well as write two new petitions (one has 119 signatures since Late Friday) and resolutions. We have only begun to receive response to these petitions.

Autism and Aluminum Exposure From Vaccines©

Many studies have been done on Autism and Thimersol (AKA Mercury) cause and effect. In many of these research papers, abstracts, and especially noted by Boyd Haley is aluminum is toxic when mixed with mercury. In this paper I will explain this connection. I will show that individuals with autism show to much aluminum in their system and show different amounts that we know are going into their bodies and show amounts. I will explain what the experts say and quote research that I have studied. These are my opinions and reflect my research into this area, allowing you the reader to make more informed decisions.
In my opinion after researching the connection of autism, aluminum, and aluminum/mercury combined theories, I have concluded that aluminum should be

removed from all vaccines. Thimersol has been removed from some vaccines, only reduced in others, and some still remain such as flu. Aluminum EDF Suspected - cardiovascular or blood toxicant, neurotoxicant, respiratory toxicant. More hazardous than most chemicals in 2 out of 6 ranking systems. On at least 2 federal regulatory lists. Aluminum phosphate - aluminum salt which is corrosive to tissues. Regarded to be harmless at one time, Aluminum is now related to serious bone and brain disorders. A high intake of aluminum affects the absorption and use of calcium, phosphorus, magnesium, selenium and fluoride. It might also lead to the development of bone deterioration. Aluminum is just as dangerous as Mercury and when combined may intensify symptoms.. Aluminum poisoning shows many of the same symptoms as Mercury poisoning, Autism, and many other illness detailed below.

Vaccine Aluminum Exposure from Birth- 2 years

Name/	Shots to 24 mo old X mg/	Lowest MG Of Al by 24 mo/		Highest MG of AL by 24 mo
Heb B	4 X .45mg	1.80 mg		1.80 mg
DTaP	5X .33mg	1.65 mg	5X ,85mg	4.25 mg
Hib	4X .225mg - 225. 0 mg	3.69 mg/		900.00 mg
Pneumococcal	5X .125mg	.625 mg		.625 mg
HepA	1X .45mg	2.80 mg		2.80 mg
Total Aluminum exposure amount		10.565 mg		909.475 mg

Not Added	
Varicella	2X
MMR	2X
Polio	4X

This amount of aluminum is given in one day and by APA and CDC standards multiple shots are given in one day increasing exposure total in the one given day,.

Aluminum National Secondary Drinking Water Regulation:

National Secondary Drinking Water Regulations (NSDWRs or secondary standards) are non-enforceable guidelines regulating contaminants that may cause cosmetic effects (such as skin or tooth discoloration) or aesthetic effects (such as taste, odor, or color) in drinking water. EPA recommends secondary standards to water systems but does not require systems to comply. However, states may choose to adopt them as enforceable standards. http://www.epa.gov/safewater/mcl.html

Contaminant	Secondary Standard
Aluminum	0.05 to 0.2 mg/L

Inorganic Chemicals MCLG1
(mg/L)2
MCL or TT1

(mg/L)2
Potential Health Effects from Ingestion of Water Sources of Contaminant in Drinking Water
Mercury (inorganic) 0.002 0.002 Kidney damage Erosion of natural deposits; discharge from refineries and factories; runoff from landfills and croplands
http://www.epa.gov/safewater/mcl.html

If an estimated 2 L (liters) is being consumed daily by adults, a corresponding 0.08 mg to 0.224 mg of aluminum is taken in per day. When broken down into 2 years increments it would represent the below chart. Figures were extracted from 7.0 HUMAN EXPOSURE http://ntp-server.niehs.nih.gov/htdocs/Chem_Background/ExecSumm/aluminum/Aluminum(7).htm

Amount of Time	2 Liters daily	Aluminum intake	Total 2 years
(2 Years) 730 days	1	0.08 mg	58.4 mg
(2 Years) 730 days	1	0.224 mg	81.76 mg

EPA recommends that the concentration of aluminum in drinking water not exceed 0.2 parts of aluminum per million parts of water (0.2 ppm) because of aesthetic effects, such as taste and odor problems. Agency for Toxic Substances and Disease Registry (ATSDR). 1999

Conclusion:
Vaccine Exposure to aluminum per any given shot far exceeds the Nation Secondary Drinking Water Level of Safety even at the lowest MG of AL. In My Opinion and many experts Aluminum should be removed from all vaccines due to toxic safety levels.

Aluminum: A fourth toxic metal (is also an additive to promote antibody response) aluminum hydroxide (allows the vaccine to stay in the body longer, stimulating the immune system for long periods, which places a strain on the immune system. Adjuvants - such as aluminum hydroxide or aluminum phosphate, are added to increase the ability of the vaccine to trigger, enhance, or prolong an immune response. Aluminum gels (or salts of aluminum) have been added to a wide range of vaccines since its discovery in 1926.

Alzheimer's and Aluminum: For years, researchers have puzzled over the surprisingly high levels of aluminum that turn up in the shriveled brains of Alzheimer's disease victims. While a growing number of investigators say that aluminum may play a central role in causing the disease that afflicts mostly elderly people. The latest evidence of a link emerged when Australian scientists reported that aluminum used to purify water accumulated in the brains of laboratory rats. The Australian study focused new interest on the issue at a time when Ottawa's environmental health directorate is preparing to propose Canada's first national guidelines for aluminum levels in drinking water. The Australian study was important, said the directorate's chief: DR BARRY THOMAS

Quote: Boyd Haley: 2nd OPTION REGARDING VACCINES WITH MERCURY PRESERVATIVES Boyd Haley: An aluminum compound was also found in many of the vaccines. Aluminum at doses of 10 micromolar will kill all these same necessary enzymes, plus do neurological damage. How much aluminum is in a vaccine? 17,500 micromolar. How can we expect our bodies, and those of babies, to survive a blast of 17,500 when 10 has already done more than enough damage. But, the worst is yet to come. The combination of mercury plus aluminum is far worse than the sum of the two toxicities added together. Many of the manufacturers have agreed to stop using thimerosal, but not until they sell the millions of vaccine doses they currently have in stock. Aluminum will have to wait for another flurry of neurological problems before it will be removed from vaccines.

Include in this the toxic effects of high levels of aluminum and formaldehyde contained in some vaccines, and the synergist toxicity could be increased to unknown levels. Further, it is very well known that infants do not produce significant levels of bile or have adult renal capacity for several months after birth. Bilary transport is the major biochemical route by which mercury is removed from the body, and infants cannot do this very well. They also do not possess the renal (kidney) capacity to remove aluminum. Additionally, mercury is a well-known inhibitor of kidney function

Further, combining thimerosal with the millimolar levels of aluminum cation plus significant levels of formaldehyde, also found in these vaccines, would make the vaccine mixture of even greater risk as a neurotoxic solution. The synergistic effects of mercury toxicity in the presence of other heavy metalS (Pb, Cd, Zn) is well established in the literature

Then, in November 1973, the company's legal division suggested adding the statement: "Do not use when aluminum may come in contact with treated skin". Aluminum is a compound added to many vaccines as a catalyst. But even with this warning, the government committees did nothing. Haley said any good biochemist knows that thimerosal and aluminum react dangerously when combined together

Boyd Haley states believes that the combination of thimerosal and aluminum in vaccines with oral antibiotics could inhibit brain development, and could be dangerous to infants in the amounts present in thimerosal-containing childhood vaccines.

For each committee member, hearing attendees, and for the general public Autism Awakening has sponsored and developed a separate website that will be linked to their main site on December 10, 2002 to alert the general public of our findings as well as put it in the online Autism In Focus free newspaper, but would like to share the link with you below. This link is also included in the book and CD. We feel some of the things in the content of those pages and website will show connections many have not yet seen, some you may be aware of.

These findings have compelled us to continue our research into other heavy metals and vaccine ingredients to find out what else we may find. We will link those findings also to this site for your convenience.

VOSI/Childscreen is polling all ACIP members on the following 4 questions and will present the results of the survey to Dan Burton with a copy to Senator Tom Harkin in order that his Government Reform Committee insures that the ACIP accepts the V50.3A standard to delay vaccinating hyper IgE newborns who have a compromised immune system.

The results of this survey will be tabulated with only the ACIP assigned member numbers used in order to protect the identity of the responders to all persons except the survey and VOSI chairmen: Kathy Blanco Childscreen chairman www.childscreen.org and Donald Meserlian, VOSI Chairman, www.voicesofsafety.com . LD Wedewer, US Autism Ambassador www.autismawakening.com , Congressman Dan Burton, http://www.house.gov/burton/ , Senator Tom Harkin, http://harkin.senate.gov/

It is my belief not only as a professional but as a parent of a child with autism that mercury or aluminum, let alone combined has more then a causal link to autism. To many papers, studies, research, abstracts, and etc. have been written showing in many ways that autism is linked to vaccine injuries. I would like to show you a few inserts from the Simpsonwood Meeting which was a meeting of 51 individuals were put together by the CDC to discuss behind closed doors the connections related to autism. These topics of discussion included Aluminum and Thimerosal, showing more then a causal link.

To give you a little bit of background I want to first establish that the quotes you are about to read are established in the Simpsonwood Meeting to be experts in their fields as quoted by Walter Orenstein, M.D. CDC's director, National Immunization Program. He states that He is Impressed with quality of expertise of the 51 Leading Most outstanding Leaders in Multiple Fields.

Below are some of the TRANSCRIPT EXCERPTS quotes that were contained in this shocking behind closed door meeting. During this meeting they were asked to keep silence of this meeting and issues brought up, the next paragraph is extracted from the Simpsonwood Meeting held in 2000.
Roger Bernier, Ph.D., CDC's associate director for science, pg. 113: "We have asked you to keep this information confidential. We do have a plan for discussing these data at the upcoming meeting of the Advisory Committee of Immunization Practices on June 21 and June 22. At that time CDC plans to make a public release of this information, so I think it would serve all of our interests best if we could continue to consider these data. The ACIP work group will be considering also. If we could consider these data in a certain protected environment. So we are asking people who have a great job protecting this information up until now, to continue to do that until the time of the ACIP meeting. So to basically consider this embargoed information. That would help all of us to use the

machinery that we have in place for considering these data and for arriving at policy recommendations.

Inside the Simpsomwood Report you will see that the also knew about the dangers of the Aluminum Connections in vaccines. Please pay close attention to the parts in bold to see these connections in the Simpsonwood Meeting. Before we begin you may want to know who these quotes were from this way as you read through the quotes it will be easy for you to refer back to who they where and their connections. Please remember that many of these individuals make vaccine policy and more.

Excerpts from SImpsonwood:

Dr. Johnston, pg. 14-15 & 19-20: Thimerosal is in many vaccine because it is a preservative and it lowers the rate of bacterial and fungal contamination that may occur during the manufacturing process, packaging and the use of vaccines in the field. It is particularly a concern in multi-dose vials because of the issue of re-entry multiple times in the vials, and it is also important in the manufacturing process for a number of vaccine including inactivated influenza and some of the earlier DPT vaccine, and is a constituent of all DPT vaccines, but not all DTAP vaccines.
There are three licensed preservative in the United States, Thimerosal, ethyl and phenol. We won't talk about the other two today, but I thought I should mention them.
Thimerosal is the most active and it has been utilized in vaccines since the 1930's.
Thimerosal functions as an anti-microbial after it is cleaved into ethylmercury and thiosalicylate, which is inactive. It is the ethylmercury which is bacterial at acidic PH and fungistatic at neutral and alkaline PH. It has no activity against spore forming organisms.
There is a very limited pharmacokinetic data concerning ethylmercury. There is very limited data on its blood levels. There is no data on its excretion. It is recognized to both cross placenta and the blood-brain barrier.
The data on its toxicity, ethylmercury, is sparse. It is primarily recognized as a cause of hypersensitivity. Acutely, it can cause neurologic and renal toxicity, including death, from overdose
Dr. Halsey made a very impassioned plea that we do carefully controlled studies to in fact address the issues specifically, and that such studies be conducted neurodevelopmentalists and environmental scientists employing specific endpoints of their study
Finally I would like to mention one more issue. As you know, the National Vaccine Program Office has sponsored two conferences on metals and vaccines. I have just recounted a summary of the mercury, the Thimerosal I vaccines. We just recently had another meeting that some of you were able to attend dealing with aluminum in vaccines. I would like to just say one or two words about that before I conclude.
We learned at that meeting a number of important things about aluminum, and I think they also are important in our considerations today. First aluminum salts, and there a number of different salts that are utilized, reduce the amount of antigen and the number of injections required for primary immunization.

Aluminum salts are important I the formulating process of vaccines, both in antigen stabilization and absorption of endotoxin.
Aluminum salts have a very wide margin of safety. Aluminum and mercury are often simultaneously administered to infants, both at the same site and at different sites. However, we also learned that there is absolutely no data, including animal data, about the potential for synergy, additivity or antagonism, all of which can occur in binary metal mixtures that relate and allow us to draw any conclusions from the simultaneous exposure to these two salts in vaccines

Dr. Weil, pg. 24: One, up until this last discussion we have been talking about chronic exposure. I think its clear to me anyway that we are talking about a problem that is probably more related to bolus acute exposures, and we also need to know that the migration problems and some of the other developmental problems in the central nervous system go on for quite a period after birth. But from all of the other studies of toxic substances, the earlier you work with the central nervous system, the more likely you are to run into a sensitive period for one of these effects, so that moving from one month or one day of birth to six months of birth changes enormously the potential for toxicity. There are just a host of neurodevelopmental data that would suggest that weve got a serious problem. The earlier we go, the more serious the problem.
The second point I could make is that in relationship to aluminum, being a nephrologist for a long time, the potential for aluminum and central nervous system toxicity was established by dialysis data. To think there isnt some possible problem here is unreal.

Dr. Egan, pg. 77: "Could you do this calculation for aluminum?"

Dr. Verstraeten, pg. 77: "I did it for aluminum Actually the results were almost identical to ethylmercury because the amount of aluminum goes along almost exactly with the mercury one."

Dr. Johnson, pg. 198: "This association leads me to favor a recommendation that infants up to two years old not be immunized with Thimerosal containing vaccines if suitable alternative preparations are available. I do not believe the diagnoses justifies compensation in the Vaccine Compensation Program at this point. I deal with causality, it seems pretty clear to me that the data are not sufficient one way or the other. My gut feeling? It worries me enough. Forgive this personal comment, but I got called out a eight o'clock for an emergency call and my daughter-in-law delivered a son by C-section. Our first male in the line of the next generation, and I do not want that grandson to get a Thimerosal containing vaccine until we know better what is going on. It will probably take a long time. In the meantime, and I know there are probably implications for this internationally, but in the meantime I think I want that grandson to only be given Thimerosal-free vaccines."
Dr. Weil, pg. 207: "The number of dose related relationships are linear and statistically significant. You can play with this all you want. They are linear. They are statistically significant. The positive relationships are those that one might expect from the Faroe Islands studies. They are also related to those data we do have on experimental animal

data and similar to the neurodevelopmental tox data on other substances, so that I think you can't accept that this is out of the ordinary. It isn't out of the ordinary."

Dr. Weil, pg. 208: "The rise in the frequency of neurobehavioral disorders whether it is ascertainment or real, is not too bad. It is much too graphic. We don't see that kind of genetic change in 30 years."

Dr. Brent, pg. 229: "The medical/legal findings in this study, causal or not, are horrendous and therefore, it is important that the suggested epidemiological, pharmokinetic, and animal studies be performed. If an allegation was made that a child's neurobehavioral findings were caused by Thimerosal containing vaccines, you could readily find junk scientist who would support the claim with "a reasonable degree of certainty". But you will not find a scientist with any integrity who would say the reverse with the data that is available. And that is true. So we are in a bad position from the standpoint of defending any lawsuits if they were initiated and I am concerned."

Dr. Meyers, pg. 231: "Can I go back to the core issue about the research? My own concern, and a couple of you said it, there is an association between vaccines and outcome that worries both parents and pediatricians. We dont really know what that outcome is, but it is one that worries us and there is an association with vaccines. We keep jumping back to Thimerosal, but a number of us are concerned that Thimerosal may be less likely than some of the potential associations that have been made. Some of the potential associations are number of injections, number of antigens, other additives. We mentioned aluminum and I mentioned yesterday aluminum and mercury. Antipyretics and analgesics are better utilized when vaccines are given. And then every body mentioned all of the ones that we can't think about in this quick time period that are a part of this association, and yet all of the questions I hear we are asking have to do with Thimerosal. My concern is we need to ask the questions about the other potential associations, because we are going to the Thimerosal-free vaccine. If many of us don't think that this is a plausible association because of the levels and so on, then we are missing looking for the association that may be the important one."

Dr. Caserta, pg. 234: "One of the things I learned at the Aluminum Conference in Puerto Rico that was tied into the metal lines in biology and medicine that I never really understood before, is the interactive effect of different metals when they are together in the same organism. It is not the same as when they are alone, and I think it would be foolish for us not to include aluminum as part of our thinking with this."

Dr. Clements, pg 247- 249 "My mandate as I sit here in this group is to make sure at the end of the day the 100,000,000 are immunized with DTP, Hepatitis B and if possible Hib, this year, next year and for many years to come, and that will have to be with Thimerosal containing vaccines unless a miracle occurs and an alternative is found quickly and is tried and found to be safe."

Dr. Bernier, pg. 256: "As difficult as science is, there are two other equally tricky, complex challenges. The policy crafting has to take into consideration some very diverse and complex issues. There is another group that will deal with that, and then we have the communication and how we handle this, which I think I am no expert at, but seems equally daunting to me as the scientific and the policy issue."

"I don't think we can set a rule here because some people have gotten these documents. For example, some of the manufacturers were privileged to receive this information. It has been important for them to share it within the company with the experts there, so they can review it. Some of you may have questions. You may have given a copy, but I think if we will all just consider this embargoed information, if I can use that term, and very highly protected information, I think that was the best I can offer."

To see 262 pages of the Simpsomwood Meeting go online to:
http://autismawakeninginia.bizland.com/autismandaluminumvaccineexposurecomparisionstudy/index.html

In Conclusion while we begin to chart a new course for the future, we need to ensure that the aluminum connection is researched fully from the new findings in the report requested to be entered into testimony. We further request that the aluminum/mercury combined cause and effects as well as safety reports and measures of responsible standards of best practices of vaccine policy, vaccine standards, testing, and funding. We need to ensure the public that when they go to bed at night they know their children and loved ones will be safe from all harm including those in vaccines. Below are a few suggestions that we believe that should be a part of charting our future.
To ensure public safety we need to remove mandatoriums of potentially deadly, vaccination of largely uninformed and non-consenting school children, new parents, college students, health workers, military personnel, and even newborn infants,

NOW WE THE PEOPLE REQUEST RESOLUTION SPONSORSHIP AND MANDITORIUM TO:

1. Government and Manufactors responsibility, accountability,and mandatory full disclosure under penility of law for non complience regarding, all CDC/NIH/APA/reports vaccine risks and injuries assoiciated with autism, Thimerisol, Aluminum, and other vaccine additives and diseases that causes or caused potiencial harm. Uphold the Right to a fair day in court, with legal and compensation funding provided to all vaccine injured individuals within no more then 1-2 months from the time the judge has ruled. Without penalty of court and hearing records being conceal.

2. 2003 SENATORIAL AUTISM HEARINGS

3. Philosophical Exemptions For vaccines In All States The right to refuse vaccinations without persecution, threatened access to schools and workplaces, or loss of jobs. Which allows children to be exempted from the immunization requirement if one parent or guardian objects in writing to the Department of Public Health, physician, minister, or school administrator because of philosophical beliefs (in addition to the already available medical and religious exemptions). For written objections based on philosophical beliefs, a notarized statement must be provided to the school administrator annuallyalong with a Vaccination Exemption Card provided by the Department of Public Health in each city and state.

4. Legislation Protecting the Rights of Due Process, Hearing, or Sealing of any information related to vaccine injured to ensure that the rights of all Americans are upheld.

5. Mandatory prescreening for all infants before vaccination for immune system errors or problems for at risk allowing or vaccine delays utilizing VOSI Standards, Child Screen Team, and other set safe standards duration in between vaccines, and new vaccine standards.

6. Requiring the removal and Immediate Recall of Aluminum or Thimersol containing vaccines

7. Increased Reseach Funding for all vaccine connections. Grant made Available to all researchers and Doctors in this field including but not limited to: Boyd Haley, Andrew Wakefield, William Walsh, Vijendra Singh, Woody McGinnis, Child Screen Team, and VOSI.
8. Iimmediate Removal of sections 1714-1717 of the Homeland Security Bill

NOW We The People therefore respectfully petition you to initiate, expedite, and/or support these investigations not only by the Congressional Government Reform but Also by a committee to be initiated in 2003 Senatorial Autism Hearings, We would like Senator Tom Harkin being of integrity, honor, fair justice, and overall humanitarian to Chair the committee. We need to enact legislation to limit toxic vaccine additives, research vaccine safety, research biological and chemical exposures of the American people, ensure fair treatment, the population safety, and welfare.
Thank you for taking the time to listen to my testimony and the words of other concerned individuals today and for entering our information into testimony. God Bless and keep up the great work!!

Written By:

LD Wedewer, US Autism Ambassador,
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In Conjunction With:

US Autism Ambassadors, Autism Awakening, Autism Help For You, Child Screen Team, VOSI, and more

To see the rest of the testimony and additions not in the book or CD go to the Testimony Website link below:

Testimony Website link:
http://autismawakeninginia.bizland.com/autismandaluminumvaccineexposurecomparisionstudy/index.html

(NOTE: we will be making additions to this site as we find out more so make sure to bookmark it on your computer.)

Vaccine Protection Act Resolution and Petition :

http://www.PetitionOnline.com/USVPAR/petition.html

http://autismawakeninginia.bizland.com/autismandaluminumvaccineexposurecomparisionstudy/id26.html

RESOLUTION CONCERNING REMOVAL OFALUMINUM ADDITIVE IN VACCINES

http://www.petitiononline.com/mod_perl/signed.cgi?NoMadVac

http://autismawakeninginia.bizland.com/autismandaluminumvaccineexposurecomparisionstudy/id3.html

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Part of Written Testimony Submitted For December 10, 2002
Hearing Titled: **Vaccines and the Autism Epidemic: Reviewing the Federal Government's Track Record and Charting a Course for the Future**
(NOTE: Rest will be mailed on CD ROM In word document and can be found online at links below. Please see changes to the Resolution in Bold)

To: Congressman Dan Burton (IN-R)
2185 Rayburn HOB
Washington, DC 20515
202-225-2276
FAX: 202-225-0016

Copy To Senator Tom Harkin (IA-D)

Vaccine Protection Act Resolution

To: US Senate, US Congress, and General Public

Vaccine Protection Act Resolution

WHEREAS Autism is a devastating disorder affecting over 1.5 million individuals, Over 3 million parents, and Over 6 million Grandparents. Many links to the vaccines have lead back to Autism such as but not limited to, Thimerosal, Aluminum, MMR Theories, and

WHEREAS vaccines developed to prevent infectious diseases researchers, parents, and professionals have found strong new links, studies, and reports that show that the immune system have in certain cases have been associated with Autism, Alzheimer's, several forms of cancers and other illnesses. There are additives, biological, and chemical agents, that currently the FDA cannot, and does not, have enough studies that proves or adequately assures the safety and efficacy of vaccines, and

WHEREAS A growing body of scientific evidence now links a variety of relatively new immune system related disorders including AUTISM, Iron overload/mal-absorption, ASPERGERS, PDD/NOS, several forms of malignant cancer, chronic fatigue immune dysfunction (CFIDS), fibromyalgia, AIDS, Gulf War syndrome, multiple sclerosis (MS), some forms of rheumatoid arthritis, diabetes, sudden infant death (SIDS suspected), hay fever, food allergies(suspected) Alzheimer's, Parkinson's (suspected), and other ailments, disorders, and diseases are related to vaccines and/or vaccine induced injuries, and

WHEREAS Thimerosal or Aluminum alone is toxic and harmful in vaccines as an additive, when combined these injuries can be more then doubled.

WHEREAS Despite official assurances to the contrary, investigations
Court Cases, and Government Reform Autism and Vaccine Hearings have shown proof to the autism and vaccine connections via Thimerosal, Aluminum, and more, and

WHEREAS MEDICAL EXEMPTIONS may be hard to obtain, even if necessary. States permit a medical exemption from vaccinations when a medical doctor certifies that a particular vaccine is contraindicated for the individual, and

WHEREAS: The following states permit a religious exemption many on the tenant of the church not the tenant of the individual belief: Alabama, Arkansas, Colorado, Connecticut, Delaware, DC, Florida, Georgia, Hawaii, Idaho, Illinois, Iowa, Kansas, Kentucky, Maine, Maryland, Massachusetts, Michigan, Missouri, Montana, Nebraska, Nevada, New Hampshire, New Jersey, New Mexico, New York, North Carolina, Ohio, Oregon, Pennsylvania, Rhode Island, South Carolina, South Dakota, Tennessee, Texas, Utah, Vermont, Virginia, Washington, Wisconsin, Wyoming, and

WHEREAS PHILOSOPHICAL EXEMPTION may be even harder to obtain. The following states permit a philosophical exemption: Arizona, California, Colorado, Idaho, Indiana, Louisiana, Maine, Michigan, Minnesota, Nebraska, North Dakota, Ohio, Oklahoma, Utah, Vermont, Washington, Wisconsin, and

WHEREAS Area's of misconception lies in the general public regarding the "religious exemption" clause. Parents are misled and are forced into submitting a letter from their place of worship stating that the church disagrees with the vaccination of children and/or adults, and

WHEREAS The assumption by some that the "religious beliefs" of an individual must be dictated by the policy of the tenant of the church is patently wrong but currently in use across the United States in over 25 states. Webster's Dictionary will not uphold this belief, but since this is a legal question, a legal dictionary should be consulted. Black's Law Dictionary provides these definitions, and

WHEREAS Black's Law Dictionary Definitions for RELIGION: "Man's relation to Divinity, to reverence, worship, obedience, and submission to mandates and precepts of supernatural or superior beings. In its broadest sense includes all forms of belief in the existence of superior beings exercising power over human beings by volition, imposing rules of conduct, with future rewards and punishments. Bond uniting man to God, and a virtue whose purpose is to render God worship due him as source of all being and principle of all government of things." (Nikulnikoff v. Archbishop, etc., of Russian Orthodox Greek Catholic Church, 142 Misc. 894, 255 N.Y.S. 653,663), and

WHEREAS Black's Law Dictionary Definitions For RELIGIOUS FREEDOM: "Within Constitution embraces not only the right to worship God according to the dictates of one's conscience, but also the right to do, or forbear to do, any act, for conscience sake, the doing or forbearing of which is not inimical to the peace, good order, and morals of society." (Barnette v. West Virginia

State Board of Education, D.C.W.Va. 47 F. Supp. 251, 253,254; Jones v. City of Moultrie, 196 Ga. 526,27 S.E. 2d 39), and

WHEREAS THE UNITED STATES CONSTITUTION The Constitution of the United States of America supports God's law, and any compulsory vaccination program is in violation thereof. It would violate the Declaration of Independence, the U.S. Constitution (Article IV and the Preamble), Articles VI, IX and X of the Bill of Rights and Article XIV of the Amendments. U.S. Constitution, Preamble: "We the people and secure the Blessings of Liberty to ourselves and our Posterity" , and

WHEREAS U.S. Constitution, Article IV, Section 2: "The Citizens of each State shall be entitled to all Privileges and Immunities of Citizens in the several States", and

WHEREAS The Bill Of Rights, Article VI: "In all criminal prosecutions, the accused shall enjoy the right to a speedy and public trial, by an impartial jury of the State and district wherein the crime shall have been committed, which district shall have been previously ascertained by law, and to be informed of the nature and cause of the accusation; to be confronted with the witnesses against him; to have compulsory process for obtaining witnesses in his favor, and to have the assistance of Counsel for his defense." (Therefore, in order for the state or federal governments to vaccinate children against the parents' authority, they would have to charge the parent under criminal laws and then try their case in court. The government cannot do that because it is a legal fiction and it would not have jurisdiction.), and

WHEREAS The Bill Of Rights, Article IX: "The enumeration in the Constitution, of certain rights, shall not be construed to deny or disparage others retained by the people.", and

WHEREAS Bill Of Rights, Article X: "The powers not delegated to the United States by the Constitution, nor prohibited by it to the States, are reserved to the States respectively, or to the people.", and

WHEREAS Amendments, Article XIV, Section 1: "No state shall make or enforce any law which shall abridge the privileges or immunities of citizens of the United States, nor shall any State deprive any person of life, liberty or property without due process of law; nor deny to any person within its jurisdiction the equal protection of the laws." GUARDIANSHIP OVER CHILDREN, and

WHEREAS The Declaration of Independence begins: "When in the course of human events, and to assume among the powers of the earth, the separate and equal station to which the Laws of Nature and of Nature's God entitles them,, and

THEREFORE, on the basis of citizens right to informed consent, we need to ensure each mother before receiving vaccinations to any child should have to go to an annual class so they can exercise their right to educated informed decisions that will effect their child's life, and

THEREBY Remove mandatoriums of potentially deadly, vaccination of largely uninformed and non-consenting school children, new parents, college students, health workers, military personnel, and even newborn infants,

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SAMPLE LETTER:
Dear Senator ____________
I urge you to support and CO-Sponsor the Vaccine Protection Act Resolution and Petition
I believe every patient has a right to their personal belief as long as they are not
breaking the law. That all individuals should be able to obtain various treatment options when conventional methods fail or after adequately gaining information as to the risk/benefits of traditional and alternative treatments.

Please protect our right to choose the best healthcare delivery system by passing this legislation. If you have not done so already, Please cosponsor this important legislation.

Senator, I believe that every citizen of this country has the right to a fair pursuit of justice when wronged. The drug companies are attempting to take away many Americans rights to freedom of choice, informed consent, and with the Vaccine amendments in the Homeland Security Bill moving forward quickly, we need to ensure that we do not take away the Constitution Rights of the people. Let's put a stop to anti-child, pro-corporation, anti-justice, and corporate welfare before that of the rights of our children, elderly, and general public. Thimerosal is a mercury-based preservative that may have damaged thousands of children, Aluminum mirrors the same effects and intensifies when combined together. These children and their families have the right to pursue this issue in court. I ask you, Senator, as a protector of our nation to choose to help our most precious national security our children

Signature ________________

Name (Print or Type)______________

Address ____________________

____

____

Please email us a copy at:
USAutismAmbasadr@aol.com

Or Postal mail us copy at:
Autism Awakening
1900 K Street SW
Cedar Rapids, Iowa 52404-3520

Send a copy to: Your US Senators and US Congressmen
To locate which Representative/Senator Online:
http://autismawakeninginia.bizland.com/ussenateandcongresscontactinformation/
Or call Autism Awakening at (319) 364-2687.

Sincerely,

The Undersigned

To Sign This Resolution Petition Located Online at link below:

USVPAR/petition.html

http://www.PetitionOnline.com/USVPAR/petition.html

LD Wedewer, US Autism Ambassador,
Joyce Minor US Autism CO-Ambassador
And Autism Awakening
1900 K Street SW
Cedar Rapids, IA 52404-3620
319-364-2687 or 319-431-8993
EMAIL: USAutismAmbasadr@aol.com
www.AutismAwakening.com

Regarding Part of Written Testimony Submitted For December 10, 2002
Hearing Titled: **Vaccines and the Autism Epidemic: Reviewing the Federal Government's Track Record and Charting a Course for the Future**
(NOTE: Rest will be mailed on CD ROM in word document or can be found online at links below)

REMOVAL OF ALUMINUM ADDITIVE IN VACCINES RESOLUTION and PETITION

To: Congressman Dan Burton
2185 Rayburn HOB
Washington, DC 20515
202-225-2276
FAX: 202-225-0016

To: U.S. Congress, U.S. Senate, General Public

WHEREAS: Thimerosal also known as Mercury was ordered to be removed from vaccines because of side effects in vaccines, increase of autism due to vaccine injury, Thimerosal toxicity, and safety factors; and

WHEREAS: Vaccines still contain Thimerosal in reduced amounts and the Flu shot still remains the same. Many doses of vaccines containing Thimerosal still remain on many shelves, and

WHEREAS: One of the foremost Leading toxicologist Boyd Haley states that any good biochemist knows that Thimerosal and aluminum react dangerously when combined together. In light of my research study into the Summary Comparison of Characteristics of Autism, Aluminum, & Mercury Poisoning© showing that aluminum and mercury in autism has almost all similar effects, symptoms, causes and may mimic other disorders such as but not limited to Alzheimer's; and

WHEREAS: Studies throughout the years show that Aluminum by itself has the same effect as Thimerosal once injected into the human body as illustrated in the attached summary chart; and

WHEREAS: An Aluminum compound also found in many of the vaccines. Aluminum at doses of 10 micromolars will kill all these same necessary enzymes as Thimerosal, plus do neurological damage. How much aluminum is in a vaccine? 17,500 micromolars and some more. How can we expect our bodies, and those of babies, to survive a blast of 17,500 when 10 has already done more than enough damage? The combination of mercury plus aluminum is far worse than the sum of the two toxicities added together. The synergist toxicity could be increased to unknown levels; and

WHEREAS: Safety testing of many vaccines is limited and the data are unavailable for independent scrutiny, so that mass vaccination is equivalent to human experimentation and subject to the Nuremberg Code, which requires voluntary informed consent; and

WHEREAS: Aluminum has been used in vaccines since around 1926-1930. In the past 5-10 years there has been an upsurge increasing growth of autism, mental disorders, and other illnesses; and

WHEREAS: There are increasing numbers of mandatory childhood vaccines, to which children are often subjected without meaningful informed consent, including information about potential adverse side effects; and

WHEREAS: Parents who exercise their freedom to refuse one or more vaccines may be subjected to penalties ranging from deprivation of the right to enroll their child in school, to threats of removing the child from parental custody and forcible vaccination; and

WHEREAS: The process of approving and "recommending" vaccines is tainted with conflicts of interest;

BE IT THEREFORE RESOLVED: That ***LD Wedewer, US Autism Ambassador, Joyce Minor, US Autism CO-Ambassador***, Autism Awakening, many parents, and professionals has called for a moratorium on removal of Aluminum in all vaccines and request resolution sponsorship from Congressman Dan Burton.

REMOVAL OF ALUMINUM ADDITIVE IN VACCINES RESOLUTION and PETITION Petition

http://www.PetitionOnline.com/NoMadVac/petition.html

For More Information Go Online To:

http://autismawakeninginia.bizland.com/autismandaluminumvaccineexposurecomparisionstudy/index.html

For New Conflicts of Interest Go Online To:

http://autismawakeninginia.bizland.com/autismandaluminumvaccineexposurecomparisionstudy/id9.html

http://autismawakeninginia.bizland.com/autismandaluminumvaccineexposurecomparisionstudy/id10.html

PROPOSED RULES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

CFR Part 333

[Docket No. 75N-0183]

Mercury-Containing Drug Products for Topical Antimicrobial Over-the-Counter Human Use; Establishment of a Monograph

Tuesday, January 5, 1982

***436** AGENCY: Food and Drug Administration, HHS.

ACTION: Advance notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing an advance notice of a proposed rulemaking that would classify over-the-counter (OTC) mercury- containing drug products for topical antimicrobial use as not generally recognized as safe and effective and as being misbranded. This notice related to the development of a monograph for topical antimicrobial drug products in general, which is part of the ongoing review of OTC drug products conducted by FDA. This notice also reopens the administrative record for OTC topical antimicrobial drug products to allow for consideration of recommendations on mercury-containing drug products that have been received from the Advisory Review Panel on OTC Miscellaneous External Drug Products.

DATES: Written comments by April 5, 1982, and reply comments by May 5, 1982.

ADDRESS: Written comments to the Dockets Management Branch (formerly the Hearing Clerk's Office) (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

William E. Gilbertson, Bureau of Drugs (HFD-510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: In accordance with Part 330 (21 CFR Part 330), FDA received on October 6, 1980 a report on OTC mercury-containing drug products for topical antimicrobial use from the Advisory Review Panel on OTC Miscellaneous External Drug Products. FDA regulations (21 CFR 330.10(a)(6)) provide that the agency issue in the Federal Register a proposed rule containing (1) the monograph recommended by the Panel, which established conditions under which OTC

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EXHIBIT
51

mercury-containing drug products for topical antimicrobial use are generally recognized as safe and effective and not misbranded; (2) a statement of the conditions excluded from the monograph because the Panel determined that they would result in the drugs' not being generally recognized as safe and effective or would result in misbranding; (3) a statement of the conditions excluded from the monograph because the Panel determined that the available data are insufficient to classify these conditions under either (1) or (2) above; and (4) the conclusions and recommendations of the Panel.

Because mercurial ingredients are marketed in OTC drug products for topical antimicrobial use, FDA has determined that the Miscellaneous External Panel's recommendations on OTC mercury-containing drug products should be included as part of the proposed rulemaking for topical antimicrobial drug products. Development of this rulemaking has been ongoing for some time.

In the Federal Register of September 13, 1974 (39 FR 33103), FDA issued an advance notice of proposed rulemaking to establish the monograph for OTC topical antimicrobial drug products. In the Federal Register of January 6, 1978 (43 FR 1210), FDA issued a tentative final monograph (notice of proposed rulemaking) for OTC topical antimicrobial drug products. In the Federal Register of March 9, 1979 (44 FR 13041) FDA reopened the administrative record and announced its intent to publish an updated (amended) tentative final monograph (amended notice of proposed rulemaking) for OTC topical antimicrobial drug products. FDA advises that it is again reopening the administrative record for OTC topical antimicrobial drug products in order to allow for the consideration of the Miscellaneous External Panel's recommendations on mercury- containing drug products. An amended tentative final monograph (amended notice of proposed rulemaking) will be published in a future issue of the Federal Register. At that time, comments received on this advance notice of proposed rulemaking concerning mercury-containing drug products will be addressed. Also, the proceeding to develop a monograph for mercury-containing drug products will be merged with the general proceeding to establish a monograph for OTC topical antimicrobial drug products. Because the Panel has recommended that mercury-containing drug products be classified in Category II, no new sections to Part 333 are being included in this advance notice of proposed rulemaking.

The unaltered conclusions and recommendations of the Panel relating to OTC mercury-containing drug products for topical antimicrobial use are issued to stimulate discussion, evaluation, and comment on the full sweep of the Panel's deliberations. The statement has been prepared independently of FDA, and the agency has not yet fully evaluated the Panel's recommendations. The Panel's findings appear in this document to obtain public comment before the agency reaches any decision on the Panel's recommendations. This document represents the best scientific judgment of the Panel members, but does not necessarily reflect the agency's position on any particular matter contained in it.

After reviewing all comments submitted in response to this document, FDA will issue in the Federal Register an amended tentative final monograph for OTC topical antimibrobial drug products, including mercury-containing drug products, as an amended notice of proposed rulemaking. Under the OTC drug review procedures, the agency's position and proposal are first stated in the tentative final monograph, which has the status of a proposed rule. Final agency action occurs in the final

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monograph, which has the status of a final rule.

The agency's position on OTC topical antimicrobial drug products will be restated when the amended tentative final monograph is published in the Federal Register as an amended notice of proposed rulemaking. In that amended notice of proposed rulemaking, the agency also will announce its initial determination whether the proposed rule is a major rule under Executive Order 12291 and will consider the requirements of the Regulatory Flexibility Act (5 U.S.C. 601- 612). The present notice is referred to as an advance notice of proposed rulemaking to reflect its actual status and to clarify that the requirements of the Executive Order and the Regulatory Flexibility Act will be considered in the amended notice of proposed rulemaking. At that time FDA also will consider whether the proposed rule has a significant impact on the human environment under 21 CFR Part (proposed in the Federal Register of December 11, 1979; 44 FR 71742).

The agency invites public comment regarding any impact that this rulemaking would have on OTC mercury-containing drug products for topical antimicrobial use. Types of impact may include, but are not limited to, the following: Increased costs due to relabeling, repackaging, or ***437** reformulating; removal of unsafe or ineffective products form the OTC market; and testing necessary, if any, to elevate Category III conditions to Category I. Comments regarding the impact of this rulemaking on OTC mercury- containing drug products for topical antimicrobial use should be accompanied by appropriate documentation. Comments will not be accepted at this time on any portion of the OTC topical antimicrobial rulemaking other than that relating to mercury-containing drug products.

In accordance with § 330.10(a)(2), the Panel and FDA have held as confidential all information concerning OTC mercury-containing drug products for topical antimicrobial use submitted for consideration by the Panel. All the submitted information will be put on public display in the Dockets Management Branch, Food and Drug Administration, after February 4, 1982, except to the extent that the person submitting it demonstrates that it falls within the confidentiality provisions of 18 U.S.C. 1905 or section 301(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(j)). Requests for confidentiality should be submitted to William E. Gilbertson, Bureau of Drugs (HFD-510) (address above).

FDA published in the Federal Register of September 29, 1981 (46 FR 47730) a final rule revising the OTC procedural regulations to conform to the decision in Cutler v. Kennedy, 475 F. Supp. 838 (D.D.C. 1979). The Court in Cutler held that the OTC drug review regulations (21 CFR 330.10) were unlawful to the extent that they authorized the marketing of Category III drugs after a final monograph has been established. Accordingly, this provision is now deleted from the regulations. The regulations now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process before the establishment of a final monograph.

Although it was not required to do so under Cutler, FDA will no longer use the terms "Category I," "Category II," and "Category III" at the final monograph stage in favor of the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and II). This document retains the concepts of

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Categories I, II, and III because that was the framework in which the Panel conducted its evaluation of the data.

The agency advises that the conditions under which the drug products that are subject to this monograph would be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 6 months after the date of publication of the final monograph in the Federal Register. On or after that date, no OTC drug products that are subject to the monograph and that contain nonmonograph conditions, i.e., conditions which would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced or initially delivered for introduction into interstate commerce. Further, any OTC drug products subjects to this monograph which are repackaged or relabeled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstbate commerce. Manufacturers are encouraged to comply voluntarily with the monograph at the earliest possible data.

Statement of the Advisory Review Panel on OTC Miscellaneous External Drug Products on Mercury-Containing Drug Products for Topical Antimicrobial Use.

A proposed review of the safety, effectiveness, and labeling of all OTC drugs by independent advisory review panels was announced in the Federal Register of January 5, 1972 (37 FR 85). The final regulations providing for this OTC drug review under § 330.10 were published and made effective in the Federal Register of May 11, 1972 (37 FR 9464). In accordance with these regulations, a request for data and information on all active ingredients used in OTC miscellaneous external drug products was issued in the Federal Register on November 16, 1973 (38 FR 31697). (In making their categorizations with respect to "active" and "inactive" ingredients, the advisory review panels relied on their expertise and understanding of these terms. FDA has defined "active ingredient" in its current good manufacturing practice regulations (§ 210.3(b)(7), (21 CFR 210.3(b)(7))) , as "any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure of any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect." An "inactive ingredient" is defined in § 210.3(b)(8) as "any component other than an 'active ingredient.' ") In the Federal Register of August 27, 1975 (40 FR 38179) a notice supplemented the original notice with a detailed, but not necessarily all inclusive, list of ingredients in miscellaneous external drug products to be considered in the OTC drug review. The list, which included ingredients described as "mercurials," was provided to give guidance on the kinds of active ingredients for which data should be submitted. The notices of November 16, 1973, and August 27, 1975, informed OTC drug product manufacturers of their opportunity to submit data to the review at that time and of the applicability of the monographs from the OTC drug review to all OTC drug products.

Under § 330.10(a)(1) and (5) the Commissioner of Food and Drugs appointed the following Panel to review the information submitted and to prepare a report on the

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safety, effectiveness, and labeling of the active ingredients in these OTC miscellaneous external drug products:

William E. Lotterhos, M.D., Chairman

Rose Dagirmanjian, Ph. D.

Vincent J. Derbes, M.D. (resigned July 1976)

George C. Cypress, M.D. (resigned November 1978)

Yelva L. Lynfield, M.D. (appointed October 1977)

Harry E. Morton, Sc. D.

Marianne N. O'Donoghue, M.D.

Chester L. Rossi, D.P.M.

J. Robert Hewson, M.D. (appointed September 1978)

Representatives of consumer and industry interests served as nonvoting members of the Panel. Marvin M. Lipman, M.D., of Consumers Union served as the consumer liaison. Gavin Hildick-Smith, M.D., served as industry liaison from January until August 1975, followed by Bruce Semple, M.D., until February 1978. Both were nominate by the Proprietary Association. Saul A. Bell, Pharm. D., nominated by the Cosmetic, Toiletry, and Fragrance Association, also served as an industry liaison since June 1975.

Two nonvoting consultants, Albert A. Belmonte, Ph.D., and Jon J. Tanja, R.Ph., M.S., have provided assistance to the Panel since February 1977. 00700000

The following FDA employees assisted the Panel: John M. Davitt served as Executive Secretary until August 1977, followed by Arthur Auer until September 1978, followed by ***438** John T. McElroy, J.D. Thomas D. DeCillis, R.Ph., served as Panel Administrator until April 1976, followed by Michael D. Kennedy until January 1978, followed by John T. McElroy, J.D. Joseph Hussion, R. Ph., served as Drug Information Analyst until April 1976, followed by Victor H. Lindmark, Pharm. D., until March 1978, followed by Thomas J. McGinnis, R.Ph.

The Advisory Review Panel on OTC Miscellaneous External Drug Products was charged with the review of many categories of drugs. Due to the large number of ingredients and varied labeling claims, the Panel decided to review and publish its findings separately for several drug categories and individual drug products. The Panel presents in this document its conclusions and recommendations on OTC mercury-containing drug products for topical antimicrobial use. The Panel's findings on other categories of miscellaneous external drug products are being published periodically in the Federal Register.

The Panel was first convened on January 13, 1975 in an organizational meeting. Working meetings which dealt with the topic in this document were held on: January 27 and 28, March 7 and 8, April 20 and 21, June 22 and 23, August 3 and 4,

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and October 5 and 6, 1980.

The minutes of the Panel meetings are on public display in the Dockets Management Branch (HFA-305) Food and Drug Administration (address above).

No individuals requested to appear before the Panel to discuss mercury-containing drug products for topical antimicrobial use, nor was any individual requested to appear by the Panel.

The Panel has thoroughly reviewed the literature and data submissions, and has considered all pertinent information submitted through October 6, 1980 in arriving at its conclusions and recommendations.

In accordance with the OTC drug review regulations set forth in § 330.10, the Panel reviewed OTC mercury-containing drug products for topical antimicrobial use with respect to the following three categories:

Category I. Conditions under which OTC mercury-containing drug products for topical antimicrobial use are generally recognized as safe and effective and are not misbranded.

Category II. Conditions under which OTC mercury-containing drug products for topical antimicrobial use are not generally recognized as safe and effective or are misbranded.

Category III. Conditions for which the available data are insufficient to permit final classification at this time.

The Panel reviewed 18 active ingredients in OTC mercury-containing drug products for topical antimicrobial use and classified all 18 in Category II.

I. Submissions of Data and Information

In an attempt to make this review as extensive as possible and to aid manufacturers and other interested persons, the agency compiled a list of ingredients recognized, either through historical use or in marketed products, as mercurial active ingredients. Fourteen ingredients were identified as follows: Ammoniated mercury, bichloride of mercury, calomel, mercuric salicylate, mercuric sulfide, mercurochrome, mercury, mercury chloride, mercury oleate, nitromersol, para-chloromercuriphenol, vitromersol, yellow mercuric oxide, and zyloxin. Notices were published in the Federal Register of November 16, 1973 (38 FR 31697) and August 27, 1975 (40 FR 38179) requesting the submission of data and information on these ingredients or any other ingredients used in OTC mercurial drug products. In addition, in the Federal Register of September 13, 1974 (39 FR 33103), the following ingredients were deferred from the OTC Antimicrobial I Panel to the Miscellaneous Topical Panel (later renamed the Advisory Review Panel on OTC Miscellaneous External Drug Products) for review: mercuric chloride (also included in the call-for-data as bichloride of mercury), ortho-chloromercuriphenol, and ortho- hydroxyphenylmercuric chloride.

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A. Submissions.

Pursuant to the above notices, the following submissions were received:

Firms and Marketed Products

Becton, Dickinson and Co., Rochelle Park, NJ 07662--Mercurochrome.

Bowman Pharmaceuticals, Inc., Canton, OH 44702--Merphol, Mercuronate, Ointment.

Corona Manufacturing Co., Atlanta, GA 30301--Corona Ointment.

Eli Lilly and Co., Indianapolis, IN 46206--Merthiolate.

Marion Health and Safety, Inc., Rockford, IL 61101--Kip Ointment, Merthiolate Swabs, Mercurochrome Swabs.

Whitehall Laboratories, New York, NY 10017--Sperti.

B. Ingredients Reviewed by the Panel.

1. Labeled ingredients contained in marketed products submitted to the Panel.

Ammoniated mercury

Merbromin

Orthohydroxyphenylmercuric chloride

Phenylmercuric nitrate

Thimerosal

2. Other ingredients reviewed by the Panel.

Calomel (mercurous chloride)

Mercuric chloride (bichloride of mercury)

Mercuric salicylate

Mercuric sulfide

Mercury

Mercury chloride

Mercury oleate

Nitromersol

Ortho-chloromercuriphenol

Para-chloromercuriphenol

Vitromersol

Yellow mercuric oxide

Zyloxin

C. Classification of Ingredients.

1. Active ingredients.

Calomel (mercurous chloride)

Merbromin

Mercuric chloride (bichloride of mercury)

Mercury, ammoniated (ammoniated mercury)

Ortho-hydroxyphenylmercuric chloride

Phenylmercuric nitrate

Thimerosal

2. Inactive ingredients.

None.

3. Other ingredients. Mercury oleate was submitted to this Panel for the treatment of psoriasis only and will be included in the Panel's recommendations on dandruff, seborrheic dermatitis, and psoriasis drug products to be published in a future issue of the Federal Register.

Mercuric oxide, yellow (yellow mercuric oxide) was reviewed as an ophthalmic anti-infective by the Advisory Review Panel on OTC Ophthalmic Drug Products in its report published in the Federal Register of May 6, 1980 (45 FR 30002).

The Panel was not able to locate nor is it aware of data demonstrating the safety and effectiveness of the following ingredients when used as OTC mercurial topical antimicrobial active ingredients. The Panel, therefore, classifies these ingredients as Category II, not generally recognized as safe and effective for this use, and they will not be discussed further in this document.

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Mercuric oxide, yellow (yellow mercuric oxide)

Mercuric salicylate

Mercuric sulfide, red (mercuric sulfide)

Mercury

Mercury chloride

Mercury oleate

Nitromersol

Ortho-chloromercuriphenol

Para-chloromercuriphenol

Vitromersol

Zyloxin

D. Referenced OTC Volumes.

The "OTC Volumes" cited in this document include submissions made by interested persons in response to the call-for-data notices published in the Federal Register of November 16, 1973 (38 FR 31697) and August 27, 1975 (40 FR 38179). All of the information included in ***439** these volumes, except for those deletions which are made in accordance with the confidentiality provisions set forth in § 330.10(a)(2), will be put on public display after February 4, 1982, in the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

II. General Discussion

Mercury is a silver-white, heavy, liquid metal with an atomic weight of 200.59. It forms alloys with most metals except iron and combines with sulfur at ordinary temperatures.

Mercury has been known to humans perhaps longer than any other metal, and humans have used it in various ways for treating illness. With the advent of the science of chemistry, new compounds of mercury were developed and used in treatment of different pathological conditions. With the advent of the science of bacteriology, mercury compounds were among the preparations chosen for antimicrobial therapy.

It has been the general course of events that, whenever a mercury compound has been tried for a particular therapeutic function, it has been used enthusiastically at first, only to be replaced eventually by a safer or more effective drug.

Elemental mercury, especially when vaporized, is toxic and readily absorbed through intact skin, the respiratory tract, and the gastrointestinal tract (Ref. 1). The mercury compounds exhibit varying degrees of toxicity, and sensitivity to these compounds is not unusual. The literature includes a number of cases of sensitivity to mercury-containing preparations ranging from topical salves and solutions to amalgam tooth fillings (Refs. 2 and 3). Both organic and inorganic mercury compounds produce allergic contact dermatitis, and cross-sensitivity has been noted (Ref. 3).

The decline in the importance of mercury in antimicrobial therapy since midcentury can be attributed more to the discovery of its lack of effectiveness for this purpose than lack of safety, however. Work done in the field of enzyme chemistry clarifying the mode of action of mercury against bacterial and fungal cells has shown that mercury compounds as a class are of dubious value for antimicrobial use (Ref. 4).

Mercuric ions combine with free sulfhydryl groups in the bacterial cells and thus deprive the cells of these sulfhydryl groups which are necessary to insure that metabolism and growth take place. The action of mercury is primarily bacteriostatic, but it may act slowly as a bactericide (Ref. 5). That is to say, mercury inhibits the growth of bacteria, but does not act swiftly to kill them (Ref. 6).

In late 1939 and early 1940, important discoveries were made showing that the bacteriostatic action of mercury can be reversed by many types of sulfur-containing compounds. Brewer (Refs. 7 and 8) formulated a culture medium, thioglycollate, which allowed the growth of anaerobic microorganisms by the use of aerobic techniques. Marshall, Gunnison, and Luxen (Ref. 9) demonstrated that the thioglycollate medium was capable of inactivating the bacteriostatic action of thimerosal and supported the growth of contaminants. Morton, North, and Engley (Refs. 10 and 11) demonstrated that inhibited bacteria are not completely killed by mercury-containing compounds. When these inhibited bacteria are cultured in sodium thioglycollate solution, growth resumes because the solution chemically removes the mercury and eliminates any residual bacteriostatic activity (Ref. 12). Intraperitoneal injections of the sodium thioglycollate culture proved fatal to mice and hemolytic streptococci were isolated from the heart's blood after death of the mice (Ref. 11). These discoveries made it necessary to reexamine all previous reports in the literature claiming a killing activity for mercurial compounds.

It has been found that, if mercury is first allowed to combine with the sulfhydryl groups in bacterial cells, growth is inhibited, but the introduction of additional sulfhydryl groups to the cell-mercury complex neutralizes this action, and growth again takes place (Ref. 6). Brewer (Ref. 13) examined a hospital's stock of sutures, some of which had been stored for up to 10 years. Some of the sutures were nonsterile even though they had been stored in a solution containing a high concentration of mercury. Viable Staphylococcus aureus were recovered from sodium thioglycollate solution after exposure to a phenylmercuric nitrate preparation for 24 hours (Ref. 14).

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The presence of serum has also been shown to reduce the antibacterial action of mercury compounds. Three hundred times more mercuric chloride, 800 times more merbromin, and 14,000 times more thimerosal were required to inactivate half the Salmonella typhosa cells suspended in 10 mL of an 80-percent serum solution than were required to achieve comparable results in the same period of time when the microorganisms were suspended in a salt solution (Ref. 15). Thus, the activity of mercury preparations as topical antimicrobial agents would be markedly affected if the microorganisms on the skin or the surface of a wound were in contact with serum, pus, or other body fluids.

In 1933 Birkhaug (Ref. 16) calculated extremely high phenol coefficients (measurements of the killing power of a compound compared to that of phenol) for mercury compounds. The method of measurement, however, was imprecise so that one could not distinguish between the bacteriostatic and bactericidal activity. Today, measurement techniques for bactericidal activity have demonstrated that the phenol coefficient for OTC mercury-containing topical antimicrobial preparations is nonexistent when their bacteriostatic action is neutralized. This has been demonstrated by Morton, North, and Engley (Ref. 11) in studies demonstrating the effect of merbromin and thimerosal on Streptococcus pyogenes and by Engley (Ref. 17) in additional studies of the effect of mercuric chloride, phenylmercuric borate, and other mercurial compounds on this strain of bacteria.

After reviewing all data and information submitted on mercury-containing products for which topical antimicrobial activity is claimed, and after a careful review of the literature, the Panel concludes that some mercury- containing preparations are not effective and others are not safe and effective for OTC topical antimicrobial use. A bacteriostatic action that is capable of being reversed by contact with body fluids and other organic matter does not constitute an effective topical antimicrobial action, and the Panel has therefore placed all mercury compounds in Category II for topical antimicrobial use.

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(4) Harvey, S. S., "Heavy Metals," in "The Pharmacological Basis of Therapeutics," 6th Ed., edited by L. S. Goodman and A. Gilman, The Macmillan Co., New York, pp. 975-976, 1980.

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III. Categorization of Data

A. Category I Conditions.

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These are conditions under which active ingredients used as OTC mercury-containing drug products for topical antimicrobial use are generally recognized as safe and effective and are not misbranded. This document contains no Category I conditions.

B. Category II Conditions.

These are conditions under which active ingredients used as OTC mercury-containing drug products for topical antimicrobial use are not generally recognized as safe and effective or are misbranded.

1. Category II ingredients.

Inorganic mercury compounds:

Calomel

Mercuric chloride

Mercury, ammoniated

Organic mercury compounds:

Merbromin

Thimerosal

Ortho-hydroxyphenylmercuric chloride

Phenylmercuric nitrate

a. Inorganic mercury compounds--(i) Calomel. Calomel (mercurous chloride) is practically insoluble in water and therefore relatively nonpoisonous for humans unless it remains in the body for a long enough time to be oxidized. Once oxidized to mercuric chloride, it is highly toxic (Ref. 1). It has been used in the past by inunction (rubbing into the skin) as a prophylactic against venereal disease and internally as a cathartic. The Panel concludes calomel may be safe as a topical antimicrobial agent, but is not effective for this purpose.

(ii) Mercuric chloride. Mercuric chloride (bichloride of mercury) is a bivalent mercury salt that exhibits a high toxicity for tissue cells, a low lethal action for microorganisms, and an inability to protect against infection (Ref. 1). The Panel concludes that mercuric chloride is not safe and not effective as a topical antimicrobial agent.

(iii) Mercury, ammoniated. Ammoniated mercury is insoluble in water and alcohol, but readily soluble in warm hydrochloric, nitric, and acetic acids. If ingested, it causes epigastric pain, nausea, and purging.

Ammoniated mercury has been used topically in the treatment of impetigo, ringworm, psoriasis, pruritus ani, pinworm, and infestations with pubic lice (Refs. 2 and 3). Prolonged use may cause chronic mercury poisoning, local pigmentation of skin and eyelids (Ref. 4), and/or hypersensitivity to mercury (Ref. 5).

Of 70 patients treated for psoriasis with ammoniated mercury, 33 showed signs of mercury poisoning (Ref. 6). The Panel concludes that ammoniated mercury is not safe for use as a topical antimicrobial agent.

b. Organic mercury compounds. Organic mercury compounds were first synthesized in an attempt to decrease the toxicity of the mercuric ion. That the attempt was not wholly successful is shown by the fact that, while merbromin and phenylmercuric nitrate have been found to be less toxic than bichloride of mercury for human epithelial cells in vitro, thimerosal was found to be more toxic (Ref. 7). The toxicities of these compounds were not in proportion to their mercury content.

Some microorganisms have exhibited a tolerance to organic mercury compounds. For example, a strain of Penicillium roqueforti resistant to phenylmercuric acetate was shown to incorporate mercury in its hyphae, thus reducing the amount of biologically active mercury in its environment and permitting other microorganisms to grow that would have been inhibited by the mercury (Ref. 8).

(i) Merbromin. Merbromin is soluble in water and alcohol but practically insoluble in acetone, chloroform, and ether. This compound produces a carmine red solution that stains the skin a deep red, not a desirable property for an antimicrobial agent, as this can mask inflammation, and inflammation is a warning sign of infection.

In a 1928 study Simmons (Ref. 9) pointed out that most of the killing action of merbromin in an alcohol-acetone vehicle was due to the vehicle. Aqueous merbromin, 2 percent, failed to kill two strains of Staphylococcus aureus in an exposure of 10 minutes and one strain of hemolytic streptococci in an exposure of 5 minutes. The cultures were killed under similar conditions by merbromin, 2 percent, in an alcohol-acetone vehicle and by the alcohol-acetone vehicle alone, which was included as a control. It was shown in 1942 that a 1:20 dilution of merbromin failed to kill Staphylococcus aureus and Escherichia coli during an exposure of 10 minutes at room temperature (Ref. 10). A 1:20 dilution is two and one-half times more concentrated than the 2-percent aqueous solution of merbromin that is marketed OTC for topical antimicrobial use.

The Panel concludes that merbromin is safe for topical use but lacks a bactericidal action and is not an effective topical antimicrobial active ingredient.

(ii) Thimerosal. Thimerosal is a cream-colored crystalline powder that is stable in air, but not in sunlight. One gram (g) is soluble in approximately 1 milliliter (mL) water and in 8 mL alcohol, but is practically insoluble in ether and benzene. At the cellular level, thimerosal has been found to be more toxic for human epithelial cells in vitro than mercuric chloride, phenylmercuric nitrate, and merbromin (Ref. 7). It was found to be 35.3 times more toxic for embryonic chick heart tissue than for Staphylococcus aureus (Ref. 11).

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Moller and Trofast (Ref. 12) demonstrated that 10 of 20 guinea pigs sensitized to thimerosal developed a delayed hypersensitivity. This production of a hypersensitivity condition in 50 percent of laboratory animals demonstrates that the substance is very allergenic and it is reasonable to expect that thimerosal will act similarly in humans.

***441** In Sweden, where thimerosal is used mainly as a preservative in vaccines and test materials and is not sold as an OTC skin disinfectant, Moller (Ref. 13) reported a mean frequency of thimerosal allergy of 3.7 percent among dermatologic patients throughout a 5-year period during which 600 to 800 patients were treated for contact allergy each year. Moller classified thimerosal a medium stong allergen in comparison to nickel and balsam of Peru, which showed an incidence of reactions of 9 percent and 7 percent, respectively. Moller also found that among healthy subjects 10 percent of school children, 16 percent of military recruits, 18 percent of twins, and 26 percent of medical students had hypersensitivity to thimerosal. He concluded that the periodic tuberculin testing of individuals in Sweden with vaccines containing thimerosal as a preservative affords an opportunity for the development of delayed hypersensitivity to thimerosal in this population.

Underwood et al. (Ref. 14) patch tested over 400 patients in which 160 patients (40 percent) showed a positive reaction to one or more of the remedies which had been applied before an initial visit to a dermatologist. Of the 160 patients, 56 (35 percent) reacted to a mercury compound, and thimerosal was responsible for 90 percent of these reactions. The North American Contact Dermatitis Group (Ref. 15) tested 1,200 subjects with 16 allergens. Thimerosal produced an incidence of 8 percent reactions and ranked third highest of the 16 allergens. Epstein, Rees, and Maibach (Ref. 16) tested a group of private dermatological patients in the western United States with 26 substances. Thimerosal had a 13.4-percent incidence of sensitivity, which was the third highest incidence of sensitivity.

It has been suggested that hypersensitivity to thimerosal may be due to the thiosalicylate portion of the molecule and not the mercury (Ref. 5); however, this has not been confirmed. Based on the above data, the Panel concludes that thimerosal is very allergenic.

A comprehensive study of several mercury compounds in 1950 (Ref. 1) showed that these compounds were bacteriostatic rather than bactericidal and that thimerosal was no better than water in protecting mice from potential fatal streptococcal infection under the conditions of the study. The streptococcal culture was added to the various mercury antimicrobial preparations; the mixture held at the temperature of skin (32 degrees to 34 degrees C) for 10 minutes; subcultured into dextrose broth, dextrose broth with 0.1 percent thioglycollate, and dextrose broth with 10 percent blood serum; and then injected intraperitoneally into mice. The latter two culture media neutralized the bacteriostatic action of the mercury compounds (Ref. 1).

The Panel concludes that thimersal is not safe for OTC topical use because of its potential for cell damage if applied to broken skin and its allergy potential. It is not effective as a topical antimicrobial because its bacteriostatic action can be reversed.

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(iii) Ortho-hydroxyphenylmercuric chloride. Ortho-hydroxyphenylmercuric chloride occurs as white to faint pink feathery crystals that are soluble in water, alcohol, and benzene (Ref. 2). It is used in burn preparations. The Panel concludes that this compound is safe for topical use in the concentration marketed for OTC use (0.056 percent). However, as a topical antimicrobial, this compound is not effective because its action is bacteriostatic rather than bactericidal (Ref. 17).

(iv) Phenylmercuric nitrate. Phenylmercuric nitrate occurs as pearly, lustrous scales that are soluble in water (1 part to about 1,250 parts water) and slightly soluble in alcohol. Against human epithelial cells in vitro, phenylmercuric nitrate was found to be less toxic than bichloride of mercury and thimerosal, but it was still very toxic (Ref. 7). Solutions of phenylmercuric salts in concentrations of 1:1,500 and greater tend to cause blistering of human skin and may act as primary skin irritants and allergens (Ref. 18). The Panel finds phenylmercuric nitrate in the concentration submitted (1:10,000) (Ref. 19) safe for topical application, but there is no evidence that this compound is an effective topical antimicrobial at this concentration.

2. Category II labeling. The Panel concludes that labeling of any OTC mercury-containing product for topical antimicrobial use is Category II because all mercury ingredients are placed in Category II.

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C. Category III Conditions.

These are conditions for which the available data are insufficient to permit final classification at this time. This document contains no Category III conditions.

Interested persons may, on or before April 5, 1982, submit to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, written comments on this advance ***442** notice of proposed rulemaking. Three copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Comments replying to comments may also be submitted on or before May 5, 1982. Received

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comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Dated: September 23, 1981.

Arthur Hull Hayes, Jr.,

Commissioner of Food and Drugs.

Dated: December 17, 1981.

Richard S. Schweiker,

Secretary of Health and Human Services.

[FR Doc. 82-7 Filed 1-4-82; 8:45 am]

BILLING CODE 4160-01-M

47 FR 436-01, 1982 WL 180230 (F.R.)

END OF DOCUMENT

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American Academy
of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

Policy Statement

Pediatrics **Volume 104, Number 3** **September 1999, pp 568-569**

JOINT STATEMENT OF THE AMERICAN ACADEMY OF PEDIATRICS (AAP) AND THE UNITED STATES PUBLIC HEALTH SERVICE (USPHS) (RE9937)

ABBREVIATIONS. FDA, Food and Drug Administration; USPHS, US Public Health Service; AAP, American Academy of Pediatrics; HBsAg, hepatitis B surface antigen; ACIP, Advisory Committee on Immunization Practices; COID, AAP Committee on Infectious Diseases.

The Food and Drug Administration (FDA) Modernization Act of 1997 called for the FDA to review and assess the risk of all mercury containing food and drugs. In line with this review, US vaccine manufacturers responded to a December 1998 and April 1999 FDA request to provide more detailed information about the thimerosal content of their preparations that include this compound as a preservative. Thimerosal has been used as an additive to biologics and vaccines since the 1930s because it is very effective in killing bacteria used in several vaccines and in preventing bacterial contamination, particularly in opened multidose containers. Some but not all of the vaccines recommended routinely for children in the United States contain thimerosal.

There is a significant safety margin incorporated into all the acceptable mercury exposure limits. Furthermore, there are no data or evidence of any harm caused by the level of exposure that some children may have encountered in following the existing immunization schedule. Infants and children who have received thimerosal-containing vaccines do not need to be tested for mercury exposure.

The recognition that some children could be exposed to a cumulative level of mercury over the first 6 months of life that exceeds one of the federal guidelines on methyl mercury now requires a weighing of two different types of risks when vaccinating infants. On the one hand, there is the known serious risk of diseases and deaths caused by failure to immunize our infants against vaccine-preventable infectious diseases; on the other, there is the unknown and probably much smaller risk, if any, of neurodevelopmental effects posed by exposure to thimerosal. The large risks of not vaccinating children far outweigh the unknown and probably much smaller risk, if any, of cumulative exposure to thimerosal-containing vaccines over the first 6 months of life.

Nevertheless, because any potential risk is of concern, the US Public Health Service (USPHS), the American Academy of Pediatrics (AAP), and vaccine manufacturers agree that thimerosal-containing vaccines should be removed as soon as possible. Similar conclusions were reached this year in a meeting attended by European regulatory agencies, the European vaccine manufacturers, and the US FDA, which examined the use of thimerosal-containing vaccines produced or sold in European countries. The USPHS and the AAP are working collaboratively to ensure that the replacement of thimerosal-containing vaccines takes place as expeditiously as possible while at the same time ensuring that our high vaccination coverage levels and their associated low disease levels throughout our entire childhood population are maintained.

EXHIBIT
2

PENGAD-Bayonne, N.J.

he key actions being taken are:

1. A formal request to manufacturers for a clear commitment and a plan to eliminate or reduce as expeditiously as possible the mercury content of their vaccines.
2. A review of pertinent data in a public workshop.
3. Expedited FDA review of manufacturers' supplements to their product license applications to eliminate or reduce the mercury content of a vaccine.
4. Provide information to clinicians and public health professionals to enable them to communicate effectively with parents and consumer groups.
5. Monitoring immunization practices, future immunization coverage, and vaccine-preventable disease levels.
6. Studies to better understand the risks and benefits of this safety assessment.

ie USPHS and AAP continue to recommend that all children should be immunized against the
seases indicated in the 1999 Recommended Childhood Immunization Schedule of the American
:ademy of Pediatrics, the Advisory Committee on Immunization Practices (ACIP) of the Centers for
isease Control and Prevention (CDC), and the American Academy of Family Physicians (AAFP).
iven that the risks of not vaccinating children far outweigh the unknown and much smaller risk, if any,
exposure to thimerosal-containing vaccines over the first 6 months of life, clinicians and parents are
couraged to immunize all infants even if the choice of individual vaccine products is limited for any
ason. Although there is a margin of safety with existing vaccines containing thimerosal, there are steps
at can be taken to increase that margin even further. Clinicians and parents can take advantage of the
:xibility within the existing schedule for infants born to hepatitis B surface antigen (HBsAg)-negative
)men to postpone the first dose of hepatitis B vaccine from birth until 2 to 6 months of age when the
fant is considerably larger. Preterm infants born to HBsAg-negative mothers should similarly receive
patitis B vaccine, but ideally not until they reach term gestational age and a weight of at least 2.5 kg.
:cause of the substantial risk of disease, there is no change in the recommendations for infants of
3sAg-positive mothers or of mothers whose status is not known.

so, in populations where HBsAg screening of pregnant women is not routinely performed, vaccination
all infants at birth should be maintained, as is currently recommended.

addition to the key actions mentioned above, the USPHS Advisory Committee on Immunization
actices (ACIP) and the AAP Committee on Infectious Diseases (COID) will be reviewing these issues
d may make additional statements.

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e recommendations in this statement do not indicate an exclusive course of treatment or serve as a standard of medical
e. Variations, taking into account individual circumstances, may be appropriate.

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:turn to Contents

MEMORANDUM

Date: September 17, 1998

From: Marion F. Gruber, Ph.D, DVRPA/OVRR

To: M.C. Hardegree, M.D., Director, OVRR
N. Baylor, Ph. D.

Through: K. Goldenthal, M.D., Director, DVRPA

Subject: POINT PAPER "PRECLINICAL REPRODUCTIVE TOXICITY STUDIES FOR VACCINES"

Purpose:

a) To obtain feedback and concurrence from OVRR and CBER upper management on the recommendations made by the maternal immunization working group with regard to reproductive toxicity study requirements for vaccines pending licensure and to obtain concurrence that these recommendations may be used in discussing reproductive toxicity study requirements with sponsors

b) To generate a working document to promote consistency among OVRR reviewers

This document does not contain detailed proposals for reproductive toxicity studies for specific vaccine products. These will be the subjects of further discussions by the maternal immunization working group provided that concurrence on the concepts contained in this document have been obtained.

==

Rationale: Maternal immunization is intended to prevent infectious disease in the vaccinee and/or young infant through passive antibody transfer from mother to fetus. Although preclinical reproductive toxicity studies prior to licensure of vaccines intended for maternal immunization and/or women of child bearing age are critical in assessing the potential for the developmental toxicity of the product, OVRR has no written policy to date addressing such requirements. In addition, the performance and design of preclinical reproductive toxicity studies for vaccines to support their use for maternal immunization has not been addressed in the scientific literature. A maternal immunization working group was formed in January of 1998 which includes scientific staff from OVRR and toxicologists from OTRR and CDER[1].

The purpose of this working group is to optimize the advice given to sponsors regarding the preclinical testing for specific

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[1] Previous attendees of the maternal immunization working group: *CBER/OVRR:* M.Gruber, M.Hardegree, N.Baylor, K.Goldenthal, D.Chandler, K.Midthun, D.Pratt, V.Johnson, J.Clifford, L.Ball, A.Geber, C.Frasch, C.Deal, L.McVittie, L.Henchal, L.Falk, M.Monser, P.Richman, B.Sheets; *CBER/OTRR:* D.Green, M.Serabian, CDER:K.Hastings

EXHIBIT

vaccine products as well as to develop comprehensive policy for reproductive toxicity study requirements for vaccines indicated for maternal immunization and/or immunization of women of childbearing age.

The following summarizes the recommendations for reproductive toxicity studies for vaccines:

Preclinical Reproductive toxicity studies for vaccines indicated for immunization of pregnant women:

Reproductive toxicity studies should be conducted for every vaccine indicated for immunization of pregnant women. These studies should be completed prior to initiation of Phase 1 clinical trials involving pregnant women.

In addition to safety trials in pregnant women pre-licensure, pregnancy registries should be established for the purpose of effectively monitoring for any adverse events experienced by the vaccinated pregnant females, as well as to track any developmental toxicities displayed by the offspring post licensure.

Preclinical reproductive toxicity studies for vaccines indicated for immunization of adolescents and adults

Reproductive toxicity studies should be conducted prior to licensure for all vaccines indicated for adolescents and adults of childbearing age due to the increasing number of vaccines that are recommended for this population even though this has not been required by OVRR in the past. This position is further supported by the fact that reproductive toxicology studies are required for some products licensed by OTRR and for the majority of products that are regulated by CDER. Further discussions will be needed regarding the stage of product development by which the preclinical reproductive toxicity evaluation should be completed.

It is recommended that pregnancy registries be established to monitor the safety of these vaccines post licensure. Of particular concern is the administration of the vaccine to pregnant individuals.

[Note that in CDER data from teratogenicity studies are generally obtained before proceeding to Phase 2 studies. All reproductive toxicity studies, to include male fertility, teratogenicity, and postnatal development, are generally conducted before initiating Phase 3 clinical trials.]

Preclinical versus clinical experience with vaccines:

Clinical data that may have been obtained from a small number of pregnant women enrolled in non-IND studies immunized with an investigational vaccine do not replace the need for comprehensive reproductive toxicity studies.

However, clinical experience derived from immunization of pregnant women may be helpful in the evaluation of the potential for any adverse outcome on the viability and development of offspring. Such information may also aid in the design/monitoring of appropriate preclinical studies.

Design of reproductive toxicity studies

Males

The potential adverse effects on male fertility should be assessed if the vaccine indication includes the male population. This is particularly important for products that are given to military forces, e.g., the Anthrax and Botulinum toxoid vaccine. However, additional discussion will be required regarding the details of the types of studies needed for these products. The ICH S5B document may serve as guidance in the design of these studies (Reproductive Toxicology: Male fertility studies, April 5, 1996, FR 15360, Vol.61, No. 67)

Females

While the type of study performed depends on the clinical indication and the product, in general, relevant information can be obtained by conducting Segment II teratology studies and/or studies designed following stages C - E of the ICH guidance document entitled "Detection of Toxicity to Reproduction for Medicinal Products" (September 22, 1994, FR 48746, Vol.59, No. 183)

It is important that a postpartum follow-up period be included in the design of the study, in order to evaluate the active immune response in the offspring following vaccination of pregnant females.

The reproductive toxicity study should be designed to include:
1) the detection of antibody production in the pregnant animal;
2) the feasibility of antibody transfer from the pregnant female to the fetus through antibody measurements in the newborn.

General Considerations

All available clinical experiences in pregnant females should be considered for any potential application to the design of reproductive toxicity studies in animals.

All data generated from prior acute or repeat dose preclinical toxicity studies should be reviewed for their possible contribution to the interpretation of any adverse developmental effects that appear in the reproductive toxicology studies.

Reproductive toxicity studies should include a dose response component in order to assess 1) the ability of a certain dose of vaccine to elicit an antibody response and 2) the effect(s) that a particular dose has on the dam and on the conceptus.

The immunization interval and frequency of immunization(s) in a reproductive toxicity should be based on the clinically proposed immunization interval and its timing, i.e., use of the vaccine at pre-conception or during the 1st, 2nd, and/or 3rd trimester.

Reproductive toxicity studies for vaccines similar in structure and/or activity to other compounds:

Although the reproductive toxicity potential of a "prototype" vaccine may have been assessed and the similarity between the "prototype" vaccine and a new investigational vaccine(s) may have been established in terms of the manufacturing process, product characterization and clinical safety, additional reproductive toxicity studies using the final clinical vaccine formulation may be necessary (e.g., 9 versus 11-valent pneumococcal conjugate vaccine; multivalent versus monovalent GBS vaccine). [Note that in CDER, reproductive toxicology studies are usually performed for every new "molecular entity", with only few exceptions.]

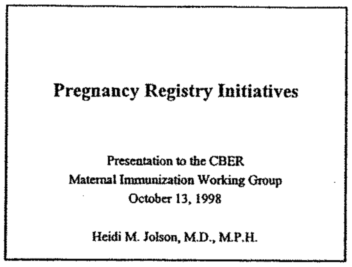
Reproductive toxicity studies should be performed for all vaccines that belong to a similar class (e.g., polysaccharide vaccines), but which contain components derived from different organisms, or where different manufacture and/or purification procedures are employed.

Use of mercury containing preservatives in vaccines intended for maternal immunization:

The FDA Modernization Act (FDAMA) of 1997, Section 413 (c)(2), states that "...regulations shall be designed to protect the health of children and other sensitive populations from adverse effects resulting from exposure to, or ingestion or inhalation or mercury."

For investigational vaccines indicated for maternal immunization, the use of single dose vials should be required to avoid the need of preservative in multi dose vials as required by the Code of Federal Regulations (CFR). Of concern here is the potential neurotoxic effect of mercury especially when considering cumulative doses of this component early in infancy. All mercury-containing vaccine formulations should be evaluated in appropriate preclinical reproductive toxicology studies that include the assessment of postnatal behavioral and developmental endpoints (This topic is being addressed by the FDA-wide working group on mercury-containing drugs).

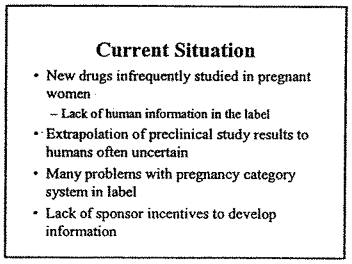
CBER/DVRPA:preparedbyMGruber(DVRPA):8/17/98



Pregnancy Registry Initiatives

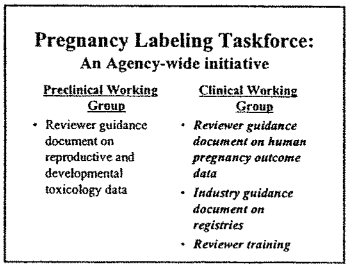
Presentation to the CBER
Maternal Immunization Working Group
October 13, 1998

Heidi M. Jolson, M.D., M.P.H.



Current Situation

- New drugs infrequently studied in pregnant women
  - Lack of human information in the label
- Extrapolation of preclinical study results to humans often uncertain
- Many problems with pregnancy category system in label
- Lack of sponsor incentives to develop information



Pregnancy Labeling Taskforce:
An Agency-wide initiative

Preclinical Working Group	Clinical Working Group
• Reviewer guidance document on reproductive and developmental toxicology data	• ***Reviewer guidance document on human pregnancy outcome data*** • ***Industry guidance document on registries*** • ***Reviewer training***

What are Pregnancy Registries?

- Prospective, active, systemic data collection
  - ***Prospective*** **- pregnancy identified before outcome is known**
  - **Sponsor recruits exposed women**
  - **Determines outcome of each pregnancy**
  - **Calculates rate of any complications/fetal abnormalities/birth defects**
  - **Comparison to rate in unexposed women**

When to Consider a Registry?

- Animal findings of concern or ambiguous
- Similarity to product previously known to be a concern
- Human findings of concern
- Expected high use of product in women of reproductive age
- Products necessary to treat a condition with high morbidity during pregnancy
- Live, attenuated vaccines (or other products causing subclinical infection)

Timing and Scope of Registries

- Consideration for phase IV commitment
- Best to initiate with product launch
- Include information on registry availability in product label
- Multiple sponsors may collaborate
- Two recent examples ...

Recent Examples: Registries as Phase IV Commitments

- Ribavirin in combination with alfa interferon
  - Indication: Hepatitis C
  - Preclinical: fetal abnormalities in all species tested
  - Category X
- Efavirenz
  - Indication: HIV
  - Preclinical: CNS abnormalities in 3/20 primates
  - Category C

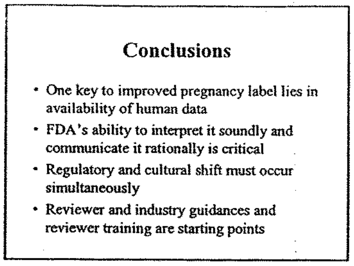
Efforts to Increase Reviewer and Industry Awareness

1 **Internal reviewer guidance document**
2 **Companion guidance document for industry**
3 **Reviewer training**
4 Discussion at outside symposia
5 Ongoing activities to redesign pregnancy section of label

(1) Reviewer Guidance

Review of Human Pregnancy Outcome Data

- Introduce major types and sources of human pregnancy outcome data
  - spontaneous reports, registries and epi studies
- Describe critical factors to consider in evaluating all pregnancy outcome data
- Review general principles of data interpretation
- Provide detailed review of pregnancy outcome data in context of 3 major data types



Conclusions

- One key to improved pregnancy label lies in availability of human data
- FDA's ability to interpret it soundly and communicate it rationally is critical
- Regulatory and cultural shift must occur simultaneously
- Reviewer and industry guidances and reviewer training are starting points

Criteri	Ranking
A. Participant enrollment • Was all enrollment prospective? • Were women actively recruited or did they initiate contact? • When was the exposure to the target drug ?	
B. Data collected at enrollment • Timing of enrollment from exposure, from identification of pregnancy? • Did they accurately assess the drug, dose, timing and extent of exposure? • What additional information was collected: indication, medical history, past pregnancies and their outcomes, socio-demographics, smoking, alcohol consumption, etc.?	
C. Data collected during follow-up • What was the method and extent of follow-up? How frequent were the contacts? • Was drug exposures and other information properly ascertained at each contact? • Did they minimize losses to follow-up? Could differential follow-up bias the results?	
D. Determination of pregnancy outcome • How and when were major anomalies ascertained for births, abortions? • How and when were minor anomalies ascertained? • How were additional and secondary outcomes defined and ascertained? • Were physical or pathological examinations conducted? How and by whom?	
E. Analysis and Interpretation • Was the risk of each outcome properly calculated with confidence intervals? • Was the minimal detectable risk (properly) estimated? • Was variation in risk assessed? Are groupings and analyses appropriate? • How do the results change if all lost had adverse outcome? None had adverse outcome? Are study results valid in light of the proportion lost to follow-up? • Does the medical condition elevate the risk of the adverse outcome? Could the drug further elevate that risk? • Relative risk - Was the comparison group appropriate? Did they compare anomaly rates among women with the same medical condition, pregnancy history, socio-demographics?	

Gruber, Marion

From: Ken Hastings 301-827-2336 FAX 301-827-2523 [HASTINGSK@cder.fda.gov]
ent: Wednesday, October 14, 1998 3:23 PM
: M CAROLYN HARDEGREE (FDACB)
: KAREN L GOLDENTHAL (FDACB); MARION F GRUBER (FDACB); Frank Sistare; Steve Hundley
Subject: Thimerosal

Sensitivity: Confidential

Carolyn: Steve Hundley, a Pharm/Tox reviewer in DSPIDP, has just about completed a review I asked him to do of the published Pharm/Tox information on thimerosal. I will forward his review to you when it is finalized, but his conclusion, basically, is that there is little in the literature to support the idea that thimerosal is a significant hazard at the doses used in vaccine products, but that there might be some "holes" in the data base that could be addressed by appropriate animal studies (e.g. repro tox, metabolism). I have had some communication with Frank Sistare, Director of Applied Pharm Research in OTR, concerning possibly doing some tox studies with thimerosal, but one issue that Frank would like some clarification on is the importance of the issue. My response was that this was probably going to be fairly important, based on the need to use thimerosal in multi-use vials, and the fact that the Europeans appear to want to essentially ban it from use in vaccines and that (I thought) there was some language in FDAMA about removing mercury-containing preservatives from drugs and biologics. I think Frank wants to get a sense of the scope of this issue before getting too involved in looking at research possibilities. an you give us some idea as to how serious this issue is?

hanx-
Ken

Maternal immunization working group
10/13/98

List of attendees

Marion Gruber	OVRR/DVRPA
Carolyn Hardegree	OVRR
Mercedes Serabian	OTRR/DCTDA
Norman Baylor	OVRR
Becky Sheets	DVRPA
Heidi Jolson	CDER/DAVDP
Karen Midthun	OVRR/DVRPA
Ken Hastings	CDER/DSPIDP
Julianne Clifford	CBER/DVRPA
LYDIA FALK	CBER/DVRPA
[illegible]	CBER/DVRPA

Brockner Ryan, Beth

From: Ball, Leslie
Sent: Thursday, October 15, 1998 9:09 AM
To: Gruber, Marion
Cc: Pratt, Douglas R.
Subject: RE: Thimerosal

Sensitivity: Confidential

Marion:

I would be happy to follow up with Dr. Hastings. I disagree about the conclusion regarding no basis for removal of thimerosal. On a strictly scientific basis, yes, there are no data that have looked at the specific issue of thimerosal in vaccines. However, there are factors/data that would argue for the removal of thimerosal, including data on methyl mercury exposure in infants and the knowledge that thimerosal is not an essential component to vaccines. In addition, the European community is moving to ban thimerosal.

Please let me know how I can get in touch with Dr. Hastings (phone number, email etc.)

Leslie

-----Original Message-----
From: Gruber, Marion
Sent: Thursday, October 15, 1998 6:12 AM
To: Ball, Leslie; Pratt, Douglas R.
Subject: FW: Thimerosal
Sensitivity: Confidential

At the re-pro tox meeting on Tuesday, we have briefly discussed the Thimerosal in vaccines issue (you'll receive the minutes shortly). K. Hastings had mentioned that somebody in his office had done a literature search and came up with the result that basically there is no scientific data base to take regulatory actions and to recommend to take thimerosal either out of vaccines or to leave it in. In fact, somebody should perform the adequate studies to come to a conclusion on the toxicity of thimerosal or its metabolized forms. There was discussion that perhaps FDA's own contract labs should perform such a study, or the National center for Toxicology research or perhaps the Office of testing and research (Frank Sistare at CDER, see below). Subsequent to our mtg, D. Hastings must have had conversations with Frank Sistare (see below). I will be out of town, and won't be able to follow up on this. My opinion is that this issue is important, new regulations.(FDAMA) give us regulatory justification to create the scientific data base from which to derive regulatory recommendations with regard to the presence of thimerosal in vaccine. I know that the two of you are actively involved in this issue. Perhaps you could follow up with Dr. Hastings. I am afraid his request for info may get lost otherwise.
-Marion

-----Original Message-----
From: Ken Hastings 301-827-2336 FAX 301-827-2523 [SMTP:HASTINGSK@cder.fda.gov]
Sent: Wednesday, October 14, 1998 3:23 PM
To: M CAROLYN HARDEGREE (FDACB)
Cc: KAREN L GOLDENTHAL (FDACB); MARION F GRUBER (FDACB); Frank Sistare; Steve Hundley
Subject: Thimerosal
Sensitivity: Confidential

Carolyn: Steve Hundley, a Pharm/Tox reviewer in DSPIDP, has just about completed a review I asked him to do of the published Pharm/Tox information on thimerosal. I will forward his review to you when it is finalized, but his conclusion, basically, is that there is little in the literature to support the idea that thimerosal is a significant hazard at the doses used in vaccine products, but that there might be some "holes" in the data base that could be addressed by appropriate animal studies (e.g. repro tox, metabolism). I have had some communication with Frank Sistare, Director of Applied Pharm Research in OTR, concerning possibly doing some tox studies with thimerosal, but one issue that Frank would like some clarification on is the importance of the issue. My response was that this was probably going to be fairly important, based on the need to use thimerosal in multi-use vials, and the fact that the Europeans appear to want to essentially ban it from use in vaccines and that (I thought) there was some language in FDAMA about removing mercury-containing preservatives from drugs and biologics. I think Frank wants to get a sense of the scope of this issue before getting too involved in looking at research possibilities. Can you give us some idea as to how serious this issue is?

1

EXHIBIT
4

The European Agency for the Evaluation of Medicinal Products
Human Medicines Evaluation Unit

CPMP/SWP/1 898/1998
8 September, 1998

SAFETY WORKING PARTY

ASSESSMENT OF THE TOXICITY OF THIOMERSAL IN RELATION TO ITS USE IN MEDICINAL PRODUCTS

Rapporteurs: Dr. Jan Willem van der Laan and Dr. Eric de Waal
Co-Rapporteurs: Dr Per Sjöberg and Dr. Ulla Liminga

CONFIDENTIAL

EXHIBIT
5

TABLE OF CONTENTS

Introduction 3

Fate in the organism 4

Toxicity 5

  Sensitisation 5
  Neurotoxicity 6
  Pre-, peri- and post natal toxicity 7
  Exposure – effect relationships 7

Existing and suggested limits for intake of organic mercury 8

Expected Exposure 9

  General population 9
  Young children 10
  Pregnant women 11

Conclusions 11

References 12

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FATE IN THE ORGANISM

Studies on the uptake and distribution of thiomersal in human and animals have shown that it is primarily taken up in the liver and kidneys but also in the brain, skeletal muscles and other organs including skin. In the body, it is mainly converted to ethylmercury and thiosalicylate as is indicated in Figure 1. The thiosalicylate substituent increases the lipophilicity of thiomersal, thereby making the intracellular compartment more susceptible to the ethylmercury residue. Ethylmercury and other alkylmercury compounds have a high affinity for sulfhydryl groups and bind to e.g. proteins or polypeptides in the organism.

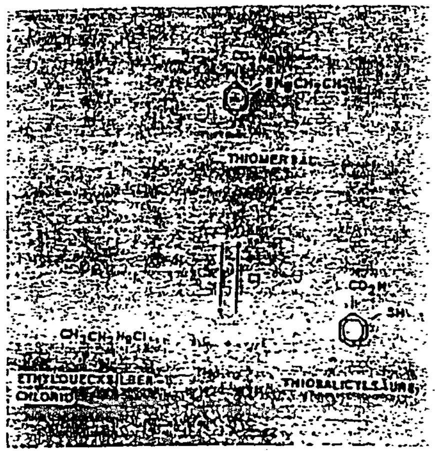

Fig. 1 Structure of thiomersal and its dissociation to form ethylmercury

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Distribution. After oral administration of methylmercury, it is distributed to all tissues within 4 days although maximum levels in the brain are only reached after 5-6 days. Concentrations are highest in hair and in a steady-state situation, hair levels may be used to estimate the body burden. In red blood cells, the concentration of methylmercury is about 10-20 times that in plasma, whereas the blood to hair ratio is about 1:250. Also ethylmercury appears to be readily distributed into all tissue compartments in appreciable amounts, including the brain.

Placental transfer of mercury-containing compounds has been studied in animals and humans. Most animal studies with methylmercury clearly show that it may accumulate in the fetus in appreciable amounts, equal or superior to those found in the mother. Studies in various species of rodents have shown that transfer of alkylmercury occurs to a higher degree than that of aryl- or inorganic mercury. Ethylmercury would appear to cross the placenta more easily than methylmercury (Leonard et al, 1983). Studies in rats suggest a peculiar affinity of mercury for the fetal brain, resulting in considerably higher

INTRODUCTION

Thiomersal (Figure 1) is an organomercuric preservative with a MW of 405, of which the mercury component accounts for about 50% (MW 201). Its antimicrobial action is related to the release of ethylmercury, after either spontaneous or enzymatic breakdown of thiomersal into ethylmercury and thiosalicylate. Thiomersal is mainly used in vaccines and immunoglobulins but is also present in other medicinal products, e.g. ophthalmologic products.

The toxicity profile of ethylmercury is very similar to that of methylmercury. Therefore, data on methylmercury are of value for the assessment of risks associated with ethylmercury. In contrast, the toxicological profiles of alkylmercury and of metallic, inorganic mercury are markedly different.

The main causes of concern with thiomersal are the induction of allergic reactions and due to the presence of ethylmercury, the potential risks of neurotoxicity. In non-pregnant adults, a Permissible Total Weekly Intake (PTWI) of 200 µg methylmercury has been recommended by the WHO (1990). At present, there is no international recommendation for a maximal intake by pregnant women or infants. There are considerable human data that indicate a higher sensitivity of fetuses and infants than of adults, due to the vulnerability of the developing brain. Furthermore, owing to the potential for tissue accumulation, administration of even low levels of ethylmercury to pregnant women will add to the overall exposure of infants. Thus, the administration of medicinal products that contain thiomersal as a preservative to pregnant women and to infants may result in an intake of alkylmercury that exceeds the levels that are considered as safe.

The aim of the present report is to assess the potential risks of the use of thiomersal-containing pharmaceuticals, especially vaccines and immunoglobulins. As data for ethylmercury are scarce the report uses the similarity in chemical properties between ethyl- and methylmercury as a starting point. For a more extensive discussion of the risks to human health of methylmercury including data on genotoxicity and carcinogenicity, reference is made to the Environmental Health Criteria 101 on methylmercury issued by the WHO in 1990.

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concentrations in fetal than in maternal brain. In humans, as in animals, it is evident that the placenta is very permeable to methylmercury (Leonard et al, 1983).

Distribution studies are not available after intramuscular or subcutaneous administration.

Metabolism and excretion. The gut is the main route of excretion; only small amounts leave the body in the urine. The rate of excretion of mercury in both humans and animals is directly proportional to the simultaneous body burden. Reports are available pointing to an average half-life of 50 days (range 39-70 days) (WHO, 1990). Early data from human and experimental animals indicated that most alkylmercury entering the body was also excreted as alkylmercury (Dales, 1972). However, other data indicate that a substantial part of the methylmercury is converted to inorganic mercury, depending on the organ. For instance, the amount found in faeces was mainly in the form of inorganic mercury (WHO, 1990).

Accumulation. Alkylmercury has a high potential for accumulation in the body at regular intake, even if the individual doses are small. Considerable experience is present from several parts of the world, enabling an approach to calculate a relationship between intake and toxicity and of acceptable levels of exposure. In case of continuous exposure, a single compartment model with a 70-day half-time predicts that the whole-body steady state will be attained within approximately one year and that the maximum amount accumulated will be 100 times the average daily intake (WHO, 1990).

TOXICITY

The main areas of concern relate to induction of sensitisation and neurotoxicity, particularly with respect to the developing brain. The effects of methylmercury in adults differ both quantitatively and qualitatively from those seen after prenatal and possibly also early postnatal exposure. Clinical and epidemiological data indicate that embryo/fetus is more sensitive to the toxic effects of methylmercury than adults. Thus, these populations need to be discussed separately.

The mechanism of toxicologic action of alkylmercury is not completely known, although considerable amounts of data are available. Mercury forms stable mercaptides with proteins containing sulfhydryl groups as well as has affinity for amino-, carbonyl- and hydroxyl groups. The WHO review (1990) indicates that protein synthesis is most sensitive to methylmercury, especially the first stage of synthesis associated with RNA transfer. This leads to a general inhibition of protein synthesis without a selective inhibition of formation of any special proteins or group of proteins.

Thiomersal has a low acute toxicity. The LD_{50} in Fisher rats was in the order of magnitude of 100 mg/kg (Mason et al, 1971). After repeated administration, the toxicity is considerably increased. For instance, in a four-week study in Fisher rats, the maximum tolerated dose was less than 5 mg/kg.

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Sensitisation

Organic mercury has been found to cause delayed-type hypersensitivity and sensitisation is a well-recognised problem of thiomersal. It is generally considered that the allergic reactions induced by thiomersal is linked to ethylmercury. However, some authors have suggested that also the thiosalicylate component may be of importance. Van 't Veen and Van Joost (1994) differentiated 3 groups of patients: (a) positive to thiomersal, but negative to mercurials and thiosalicylic acid; (b) positive to thiomersal and some other mercurials, but negative to thiosalicylic acid; (c) positive to thiomersal and thiosalicylic acid, but negative to other mercurials.

The route of administration also appears to be of importance for the sensitisation potential, where the intra- and epicutaneous routes of administration are associated with a much higher risk for sensitisation than the subcutaneous and intramuscular routes. Förström et al (1980) described 96 patients in Finland with a positive reaction to thiomersal on epicutaneous testing. Twenty percent of 45 thiomersal-sensitive eczema patients developed a reaction after subcutaneous administration of thiomersal (50 µg). It is not fully clear why the incidence was much higher in this study than data referred by Van 't Veen and Van Joost, 1994, where a Tick Borne Encephalitis (TBE) vaccine containing 50 µg thiomersal was given intramuscularly to thiomersal-hypersensitive patients with clinical eczema. In this study, only 2 out of 65 patients developed untoward reactions at the injection site. These differences might be due to the fact that different routes of administration were used. Data from Austria, where a growing number of individuals have been immunised against TBE since 1974, indicate that there is a parallel increase in the number of individuals sensitised to thiomersal (Van 't Veen and Van Joost, 1994)

From earlier data it is suggested that allergic contact eczema induced by thiomersal is rare in Europe. This may be due to its infrequent external use. The frequency of positive epicutaneous test reactions varied from 1.3% in Denmark and the Netherlands to 13.4% in the USA (Förström et al, 1980; Van 't Veen and Van Joost, 1994), which may be related to the fact that a large number of topical OTC products containing thiomersal are available in the USA.

Products containing thiomersal may also cause photohypersensitivity to piroxicam, probably as a result of cross-reactivity between thiosalicylate and a degraded photoproduct of piroxicam. In a study with 2461 patients, 32 (1.3%) had a positive patch test to thiomersal The highest number of positive reactors fell into the 4th and 5th decades of life.

Neurotoxicity

In cases of alkylmercury poisoning, neural tissue is clearly the target organ of toxicity and the central nervous system is critically sensitive to alkylmercury. The mechanism of this selective damage is not well understood.

Data from human subjects and experimental animals suggest that at least two to three weeks (sometimes several months) elapse between the beginning of exposure and the onset of symptoms. The first symptoms are paresthesia, such as numbness and tingling of fingers, toes, nose and lips, furthermore, slight tremor, headache, fatigue, difficulty in concentration and emotional lability may occur. Mild cases progress no further. For a more detailed description of symptoms for intoxication, see the WHO Review (1990).

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Pre-, peri- and post natal toxicity

Human data on pre-, peri- and post natal toxicity induced by thiomersal alone are limited. In a review published in "Birth Defects and Drugs in Pregnancy" (Heinonen, 1977), an overview of 3.482 children with any malformation in relation to exposure to Topical Antimicrobial Drugs has been presented. Out of 2,918 Mother-Child pairs exposed to antimicrobial agents, 56 pairs were exposed to thiomersal (as ophthalmologic product?) and 6 children showed signs of malformation. Although the number of cases was too small to draw any firm conclusion, the authors concluded that thiomersal was associated with an overall increase of malformations but no rise in specific abnormalities could be identified. No data are available to estimate any measure of exposure.

In contrast to the limited amount of data on thiomersal, there is considerable amount of information on fetal effects of alkylmercury compounds. In the mid-1960s", there was an outbreak of cerebral palsy and microcephaly in newborns from the fishing village of Minimata Bay, Japan (Matsumoto, et al, 1965;). These abnormalities were caused by methylmercury contamination of the fish in the bay. Similar types of intoxication occurred in Iraq after seed grain contaminated with methylmercury was mistakenly used to make bread (Marsh et al, 1980, Amin-Zaki et al, 1976). In this population, infants exposed *in utero* demonstrated psychomotor retardation and cerebral palsy. Similar congenital neurologic disease has been reported in other instances of mercury food contamination.

Experimental animal models of organic mercury embryotoxicity have associated prenatal exposures with a variety of different birth defects, many not seen in human case reports. However, the neurologic effects are generally consistent with the human experience.

Exposure – effect relationships

In the WHO review (1990), data and calculations on exposure-effect relationships for methylmercury were presented. These are summarised in this section.

Data from humans and experimental animals indicate that serious neurotoxicity from alkylmercury commonly occurs at brain concentrations as low as 10 mg/kg, which in humans correspond to a blood mercury concentration of 500 to 1000 µg/l. Blood levels of 100-200 µg/l have not been associated with any symptoms. For reference, 95 % of persons with no known exposure to mercury have blood concentrations below 40 µg/l. Overall, total mercury levels in blood are regarded as a valuable tool for assessing exposure to alkylmercury. A level of 100 µg/l has been proposed as the maximum permissible blood concentration.

The Iraqi data indicated that an intake in adults of 50 µg/day (0.83 µg/kg/d in a 60 kg adult) was associated with a 0.3% risk of developing paresthesia. This is similar to the background frequency of paresthesia and can thus be regarded as a NOAEL (No-Adverse Effect-Level). At an intake of 200 µg/day (3.3 µg/kg/day, 60 kg adult), the risk was about 8 %. A long-term intake of 3-7 µg/kg/d in adults was estimated to cause adverse effects on the nervous system, manifested as an approximately 5% increase in the incidence of paresthesia and can be regarded as a Lowest Observed Adverse Effect

Level (LOAEL). Such intake would result in blood concentrations of 200-500 µg Hg/l and peak hair concentrations of 50-125 µg/g. Japanese data show that the (first) effects are estimated to occur at levels of 200 µg Hg/l in blood and 80-100 µg Hg/g in hair. It should be pointed out that the background frequency of these non-specific symptoms plays a key role for the accuracy of these estimates. Furthermore, the estimated paresthesia frequency below intakes of about 200 µg/day are extrapolations beyond the observed data and assume the absence of a population threshold.

The WHO (1990) has summarised the data on prenatal exposure as follows:
Severe derangement of the developing central nervous system can be caused by prenatal exposure to methylmercury. In the Iraqi outbreak, the lowest level (maximum maternal hair mercury concentration during pregnancy) at which severe effects were observed was 404 µg/g. The highest no-observed-effect level (NOEL) for severe effects was 399 µg/g. Fish-eating populations in Canada and New-Zealand have also been studied. No severe prenatal effects were seen, but exposure levels were far below the highest NOEL for severe effects in Iraq.

Evidence of psychomotor retardation (delayed achievement of developmental milestones, a history of seizures, abnormal reflexes) was seen in the Iraqi population at maternal hair concentrations well below those associated with severe effects. A statistical analysis revealed that motor retardation rose above the background frequency at maximum maternal hair mercury levels during pregnancy of 10-20 µg/g. This range of concentrations in maternal hair is consistent with all available evidence and can be accepted as the range of critical concentrations. The Canadian study found that maternal hair levels were positively associated with abnormal muscle tone or reflexes in boys, but not in girls (the highest maximum maternal hair level during pregnancy was 23.9 µg/g). The New Zealand study found evidence of developmental retardation in 4-year old children at average maternal hair mercury levels during pregnancy ranging from 6-86 µg/g (the second highest value was 20 µg/g). The New Zealand mercury values should be multiplied by 1.5 to convert them to maximum maternal hair levels in pregnancy.

EXISTING AND SUGGESTED LIMITS FOR INTAKE OF ORGANIC MERCURY

At present, there are no recommendations regarding limits of ethylmercury intake. Due to the similarity between ethylmercury and methylmercury, the recommendations for methylmercury will be presented below. The IPCS report (WHO, 1990) states that the previous recommendation made by the JECFA (Joint Expert Committee on Food Additives) of a premissable tolerable weekly intake (PTWI) of 200 µg methylmercury (0.48 µg/kg/day for an adult of 60 kg) in adults remains. This should be compared with the estimated LOAEL (3.3 µg/kg/d) and NOAEL (0.83 µg/kg/d) for the occurrence of paresthesia (See Section 'Exposure – effect relationships').

With respect to pregnant women, the JECFA considered the available data to be insufficient for the determination of a PTWI. In the WHO report (1990), a maternal hair mercury concentration of 10-20 µg/g was considered critical since the frequency of motor retardation in children began to increase at those levels (based on the Iraq data). When comparing these data with the hair mercury concentrations associated with paresthesia in adults (50-125 µg/g), is appears that adverse effects in children that had

In the WHO report (1990), it was concluded that the general population does not face a significant health risk from methylmercury, although certain groups with a high fish consumption may attain blood methylmercury levels that are associated with an increased risk of neurological adverse effects in adults. Based on that and on an estimation of the normal use of thiomersal-containing medicinal products, it can be concluded that the risk for neurological adverse effects following the use of such products in non-pregnant adults is low.

Young children

In young children, mercury intake via food is difficult to estimate. Based on a 10-fold lower intake than in adults (i.e. 2.3 µg absorbed /day), an intake via food during the first year is estimated to approximately 80-100 µg methylmercury/year. Thus, in relation to the suggested total 'allowed' intake during the first year of 200-230 µg (See Section EXISTING AND SUGGESTED LIMITS FOR INTAKE OF ORGANIC MERCURY), the intake of organic mercury from other sources should not be higher than 120-130 µg during the first year of life.

National Immunisations programs in the European Union (EU) Member States

In Table 2, an overview of the maximum exposure to *ethylmercury* via vaccines containing thiomersal administered during the first and second years of age when using the National Immunisations programs in the European Union (EU) Member States is given. As evident from Table 2, there are large differences between the different National immunisation programs with respect to the administration of thiomersal-containing vaccines. The highest ethylmercury intake in any Member State during the first 12 months is about 200 µg (240 µg including TBE) and during the first 24 months about 275 µg (300 µg including TBE). Thus, in addition to the estimated intake of about 80-100 µg alkylmercury via other sources such as food (See above), these data indicate that the proposed limit of 200-230 µg/year will be exceeded by about a factor of 2, when applying certain National Immunisation programs.

Table 2: Summary of Maximum Potential Ethylmercury Exposure from thiomersal containing vaccines in National Immunisation Programs in 1st and 2nd year of age

Member State	Up t: [illegible] year of age	Up to 2 years of age (includ. 1st year)
Austria	0.165 mg (0.238 with tick borne encephalitis vaccine)	0.225 mg (0.3 mg with TBE)
Belgium	0.2 mg	0.275 mg
Denmark*	0 mg	0 mg
Finland	0.075 mg	0.1 mg
France	0.181 mg	0.25 mg
Germany	Not calculated	Not calculated
Greece	Not calculated	0.25 mg
Ireland*	0 mg	0 mg
Italy	Not calculated	0.113 mg
Luxembourg	0.063 mg	0.075 mg
Netherlands*	0 mg	0 mg
Portugal	0.075 mg	0.1 mg
Spain	0.3 mg	0.18 mg
Sweden*	0 mg	0 mg

UK	Not calculated	0.15 mg

* There are no vaccines containing thiomersal in these national immunisation programs

Treatment of immunodeficient children

Another risk category is the group of immune deficient children which are treated with immunoglobumin solutions containing thiomersal. Two clinical indications may require the administration of huge amounts of immunoglobulins in infants, i.e. "severe combined immune deficiencies" and "agammaglobulinaemia". The recommended dose of immunoglobulins is 50mg/kg/ week.

In such a case a child of 10 kg may be dosed with 500 mg immunoglobulin. If the concentration is about 16%, then a volume of 3-4 ml/10 kg will be injected on a weekly basis. The concentration of thiomersal in this product can be 0.3 mM, resulting in a dose of 200-260 µg thiomersal/week i.e 100 - 130 µg Hg/week, which is similar in one week to the total permissible yearly intake for mercury in infants below 1 year. (Example taken from the Netherlands).

Pregnant women

Another risk population is clearly pregnant women. In general, vaccinations are not recommended during pregnancy but it may be unavoidable in certain cases. Another source of thiomersal may be the administration of immunoglobulins, e.g. an anti-rubella immunoglobulin in case of a rubella infection which in itself is associated with an increased teratogenic risk. As outlined in Section 'EXISTING AND SUGGESTED LIMITS FOR INTAKE OF ORGANIC MERCURY', intake by a pregnant woman of 40 µg/week may be an acceptable level. However, since these estimations are based on continuous administration, a single administration of 50 - 75 µg ethylmercury via a thiomersal-containing vaccine or immunoglobulin may be acceptable if it occurs only once during pregnancy.

CONCLUSIONS

1. There is ample evidence from the literature that thiomersal may cause sensitisation and subsequent allergic reactions. The implications of this in relation to the use of thiomersal as a preservative in any medicinal product, should be evaluated by appropriate experts.

2. The use of thiomersal in vaccines given to infants in accordance with various national vaccination programs may in certain cases result in approximately 2 times higher intake of ethylmercury during the first year of life than what can be considered as reasonably safe. Given the great uncertainty of the estimations of safe levels in young children, it is suggested to restrict the use of thiomersal in vaccines as a precautionary measure. Since restrictive measures on the use of thiomersal in vaccines within the EU would have wider international consequences, the use of thiomersal as preservative in vaccines may need to be discussed with appropriate international bodies.

3. Various other medicinal products, e.g. immunoglobulins and ophthalmological products, are also preserved with thiomersal. Due to the particular concerns related to the exposure to organic mercury during pregnancy, the use of any thiomersal-containing product in pregnant women should be reconsidered. Furthermore, the

use of thiomersal-containing immunoglobulin products in immune deficient children should be avoided.

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Annex 4

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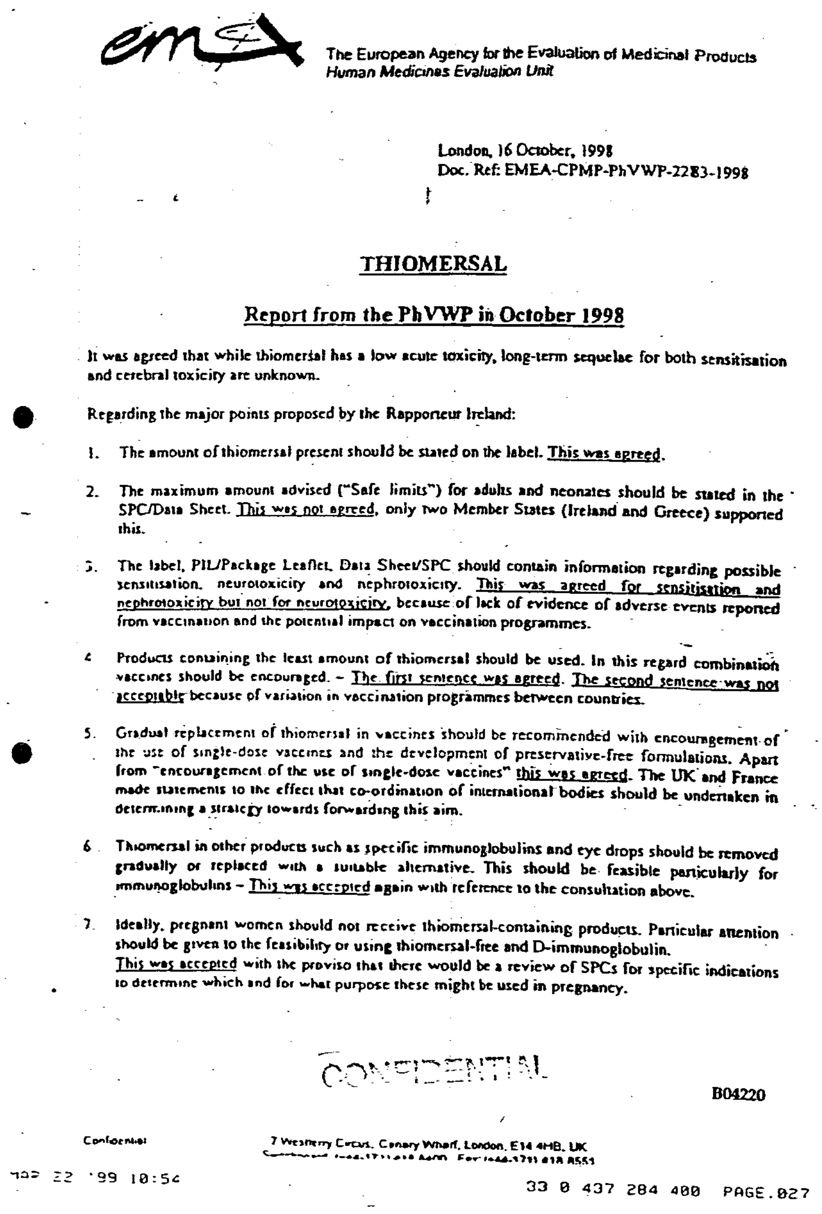

The European Agency for the Evaluation of Medicinal Products
Human Medicines Evaluation Unit

London, 16 October, 1998
Doc. Ref: EMEA-CPMP-PhVWP-2283-1998

THIOMERSAL

Report from the PhVWP in October 1998

It was agreed that while thiomersal has a low acute toxicity, long-term sequelae for both sensitisation and cerebral toxicity are unknown.

Regarding the major points proposed by the Rapporteur Ireland:

1. The amount of thiomersal present should be stated on the label. This was agreed.

2. The maximum amount advised ("Safe limits") for adults and neonates should be stated in the SPC/Data Sheet. This was not agreed, only two Member States (Ireland and Greece) supported this.

3. The label, PIL/Package Leaflet, Data Sheet/SPC should contain information regarding possible sensitisation, neurotoxicity and nephrotoxicity. This was agreed for sensitisation and nephrotoxicity but not for neurotoxicity, because of lack of evidence of adverse events reported from vaccination and the potential impact on vaccination programmes.

4. Products containing the least amount of thiomersal should be used. In this regard combination vaccines should be encouraged. – The first sentence was agreed. The second sentence was not acceptable because of variation in vaccination programmes between countries.

5. Gradual replacement of thiomersal in vaccines should be recommended with encouragement of the use of single-dose vaccines and the development of preservative-free formulations. Apart from "encouragement of the use of single-dose vaccines" this was agreed. The UK and France made statements to the effect that co-ordination of international bodies should be undertaken in determining a strategy towards forwarding this aim.

6. Thiomersal in other products such as specific immunoglobulins and eye drops should be removed gradually or replaced with a suitable alternative. This should be feasible particularly for immunoglobulins – This was accepted again with reference to the consultation above.

7. Ideally, pregnant women should not receive thiomersal-containing products. Particular attention should be given to the feasibility or using thiomersal-free and D-immunoglobulin.
This was accepted with the proviso that there would be a review of SPCs for specific indications to determine which and for what purpose these might be used in pregnancy.

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8. Thiomersal in influenza vaccine not only performs the expected function of preventing the vaccine from contamination but also is said to prevent unacceptable amounts of endotoxin developing. Thus inevitably removing thiomersal can modify solubility, antigenicity, immunogenicity and stability. However with the current availability of thiomersal-free vaccines this problem can obviously be overcome.
   This was accepted within the framework of consultation with appropriate bodies to determine strategy.

9. As proposed by the PhVWP, consultation should take place with the European Pharmacopoeia, WHO and manufacturing organisations, particularly with regard to the impact of thiomersal-containing compounds in other jurisdictions.
   This was accepted.

27/8/1998

To all members of the Pharmacovigilance Working Party

The organomercurial thiomersal (ethylmercurithiosalicylic acid) as a preservative in medicinal products

Introduction

Thiomersal is an organomercuric compound containing 50% of its molecular weight as mercury. As a preservative it fulfills the Pharmacopoeia standards and is considered by the Ph. Eur. as a 'necessary' component of multidose preparations of vaccines, eye drops and immunoglobulins. Thiomersal is contained mainly in the latter but it is also present in nasal and topical cream preparations. The safety of its use has been questioned because of:

Possible perinatal toxicity, particularly cerebral toxicity.
Sensitization properties.

In April 1998 the CPMP as part of its review of the safety of thiomersal and other organomercurials as preservatives in pharmaceuticals posed two objectives to the PvWP as follows:

- The risk of neurological effects in children when thiomersal is administered as an excipient in the different types of medicinal products: Vaccines, immunoglobulins and eye preparations, should be evaluated.
- There is ample evidence from the literature that thiomersal may cause sensitization and subsequent allegic reactions, the clinical implications in relation to the use of thiomersal as an excipient in medicinal products should be evaluated.

Background

Based on WHO data (on methylmercury derived from epidemiological studies) a total allowable exposure of 200µg of mercury during the first year of life and 200µg per week in the adult has been considered as possible 'safe limits'. Food intake plus iatrogenic sources would both be included in the allowable exposure. To calculate the amount of mercury ingested in food is difficult. In the adult this is mainly in fish or fish products. The amount during the first year of life has been estimated as 80µg leaving a iatrogenic limit of 120µg per year. Is 200 µg per year a 'safe' limit during the first year of life? That question is difficult but animal (monkey) studies indicate that total thiomersal of 41 - 2280µg (Hg content 207 - 1125µg) given intranasally over six months produced no evidence of toxicity.

Alkyl mercury can pass through the lung alveolar tissue, through intact skin and is readily absorbed from the G.I tract. Once in the body it finds few barriers and passes readily into the cerebrum, liver, lung and red cells and into almost all tissues. Because of its slow n e

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of excretion alkyl mercury has a considerable potential for accumulation in the body. A major target organ is the central nervous system. Significant exposures may cause neurological disturbances and in severe cases, cerebral palsy and microencephaly. It crosses the placenta more readily than other forms of mercury and foetal tissue concentrations may exceed those in maternal tissues. Embryotoxicity and teratogenicity of mercury taken in the diet has been described in fish, birds and mammals.

Alkyl mercury has a strong affinity for amino acid sulfhydryl groups and quickly become bound to proteins or polypeptide chains. It can also inhibit sulfhydryl group-enzymes an may act directly upon DNA replication and protein synthesis. Chromosome fragmentatio has been observed. Electron microscopy techniques have shown that organic mercurials bind to plasma membranes, lysosomes, endoplasmic reticulum, golgi, mitochondria and nuclear envelope. Some cellular degeneration could be due to the disruption of such membrane structures rich in thiol groups.

Vaccination in the neonate

Vaccination programme regimens have been reviewed from all of the EU Member States Vaccination schedules using thiomersal-containing vaccines (diptheria, tetanus, pertussis, haemophilus infleunza) takes place in most EU Member States between 2 and 6 months. It is noted that 4 countries do not use thiomersal-containing vaccines in their national immunisation programmes). In addition, in some countries hepatitis B and tick-borne encephalitis vaccines containing thiomersal may also be given during the first year of life While most EU Member States (except possibly Austria) would administer an amount of thiomersal per year within the accepted limit, if one considers that at 6 months D/T/ /P HIB will have been administered either as monocomponent or combination vaccines, th half-yearly limit may well be exceeded when allowance is made for possible mercury content in the diet.

Eye drops and Immunoglobulins

The concentration of thiomersal when present in eye drops or immunoglobulins is of the order of 0.01%. The total amount in any individual obviously depends on the volume used but in adults is unlikely to exceed 200μg of mercury per week. The use of eye drops or immunoglobulins containing thiomersal in the neonate could appreciably increase the exposure to mercury. While the number of vaccinations during pregnancy is limited, exposure to rubella might involve treatment with immunoglobulin and rhesus-negative mothers who receive thiomersal-containing anti-D immunoglobulin might be exposed to 50μg of mercury.

Sensitization/Autoimmunity

Thiomersal is one of the most frequent sensitizers throughout the world. For the most part it would appear that the ethylmercury part of the molecule is the allergic determinant. Some patients show positive reactions to the thiosalicylic component only while others react to thiomersal itself but not to inorganic or metallic mercury products or thiosalicylate. I general there is no cross-reaction between thiomersal and mercury except in those cases

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where mercury chloride was the allergic determinant responsible for sensitization to thiomersal. Thiomersal may show cross-reactivity between the thiosalicylic acid and piroxicam, causing photohypersensitivity to the latter. Sensitization is most likely provol :d by immunization with thiomersal-containing vaccines. In Europe, frequencies of positive reactions have been reported to range between 6.9% in Germany to 1.3% in Denmark. (The low figure for Denmark probably relates to the fact that Denmark has never used thiomersal in its national immunization programme). Even in sensitized patients thiomersal-induced side effects due to vaccination have not been shown to be a severe ris and patch-testing positivity to thiomersal does not represent a contraindication to immunization with thiomersal-containing vaccines particularly when the deep subcutaneo s or intramuscular route is used since there is a lower risk of sensitization with these route:

Hypersensitivity to thiomersal is more frequent amongst healthy young people than amon ; eczematous patients and is more frequent in women. Severe reactions to thiomersal are uncommon and allergic contact eczema is rare. Mercury has been implicated in autoimmune processes e.g. immune complex glomerulonephritis. The mechanism by which it does this is unknown. It may be by altering the antigenicity of cellular proteins rendering them "foreign" to the host, however mercury may also interfere with immunor regulatory cells resulting in the generation of an anti-self response, with decrease of the suppressor T lymphocyte balance necessary for preventing the formation of anti-self antibodies. Such a reaction could have consequences on the ability of the host to withstand viral attack.

Clinical significance of sensitization
Although topical reactions including skin reactions and eye allergies have been reported, n general these have not been severe and while acute anaphylaxis after intramuscular immunoglobulin has been reported this appears to be an infrequent occurrence. Nevertheless type II and IV hypersensitivity reactions do occur particularly in the young healthy and female patient and while thiomersal has a low acute toxicity, the possibility t at exposure to very small doses may have subtle but significant chronic health effects cannc be excluded since accumulation of ethylmercury may occur with repeated administration

Neurotoxicity
The central nervous system is extremely sensitive to alkyl mercury. Significant exposure may cause neurological disturbances and in severe cases, cerebral palsy and microencephaly. This point is extensively discussed in the WHO review (1990) howeve it is noteworthy that calculations indicate that an intake of 50μg/day of mercury In an adt : would involve a risk of about 0.3%, of the occurrence of symptoms of paresthesia, the f st symptoms of neurotoxicity. Bearing in mind that a neonate could receive three stat. dos ; of 25μg each of mercury during vaccination in the first four to six months of life and th : accumulation of ethylmercury can occur, the risk of toxicity may be higher in this age group.

In summary while thiomersal has a low acute toxicity the long-term sequelae for bo h sensitization and cerebral toxicity are unknown.

N°4125 E. 2/16

cc. L. Kuyken.

The European Agency for the Evaluation of Medicinal Products
Human Medicines Evaluation Unit

BIOTECHNOLOGY WORKING PARTY
MEETING ON 13-14 October 1998
Chairman: Prof. G. Vicari

Thiomersal

Final BWP report to the CPMP dated 11 September 1998

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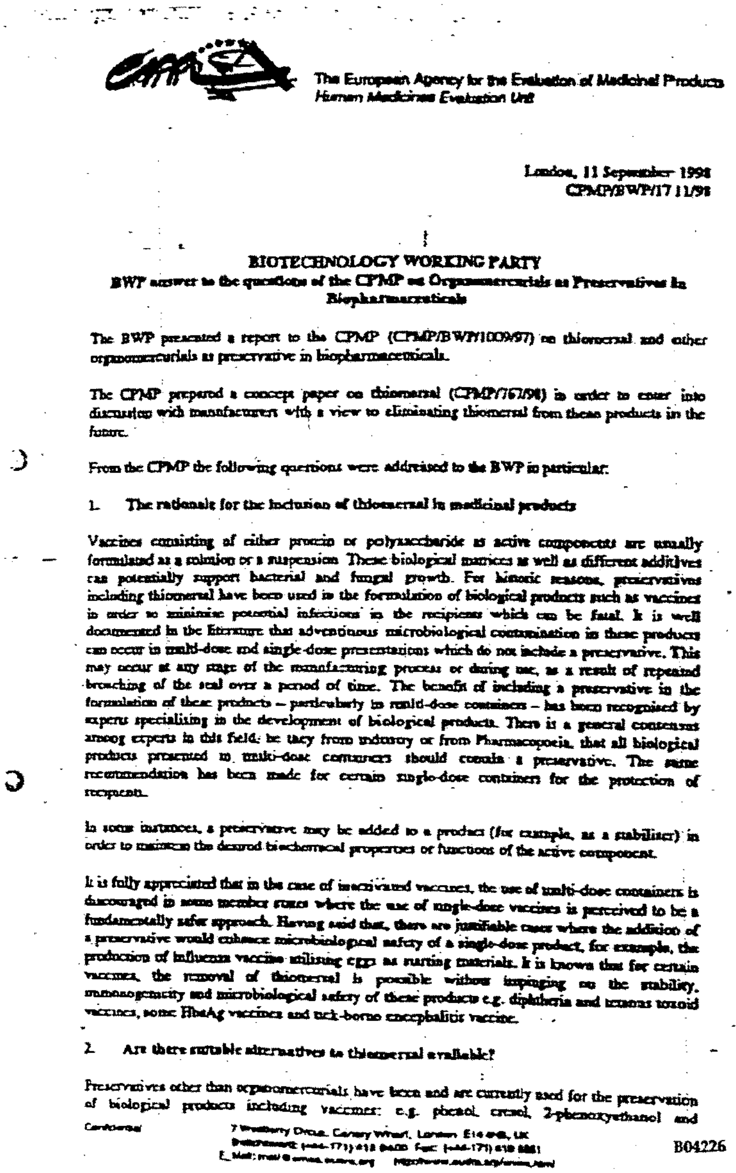

The European Agency for the Evaluation of Medicinal Products
Human Medicines Evaluation Unit

London, 11 September 1998
CPMP/BWP/17 11/98

BIOTECHNOLOGY WORKING PARTY

BWP answer to the questions of the CPMP on Organomercurials as Preservatives in Biopharmaceuticals

The BWP presented a report to the CPMP (CPMP/BWP/1009/97) on thiomersal and other organomercurials as preservative in biopharmaceuticals.

The CPMP prepared a concept paper on thiomersal (CPMP/767/98) in order to enter into discussion with manufacturers with a view to eliminating thiomersal from these products in the future.

From the CPMP the following questions were addressed to the BWP in particular:

1. The rationale for the inclusion of thiomersal in medicinal products

Vaccines consisting of either protein or polysaccharide as active components are usually formulated as a solution or a suspension. These biological matrices as well as different additives can potentially support bacterial and fungal growth. For historic reasons, preservatives including thiomersal have been used in the formulation of biological products such as vaccines in order to minimise potential infections in the recipients which can be fatal. It is well documented in the literature that adventitious microbiological contamination in these products can occur in multi-dose and single-dose presentations which do not include a preservative. This may occur at any stage of the manufacturing process or during use, as a result of repeated breaching of the seal over a period of time. The benefit of including a preservative in the formulation of these products – particularly in multi-dose containers – has been recognised by experts specialising in the development of biological products. There is a general consensus among experts in this field, be they from industry or from Pharmacopoeia, that all biological products presented in multi-dose containers should contain a preservative. The same recommendation has been made for certain single-dose containers for the protection of recipients.

In some instances, a preservative may be added to a product (for example, as a stabiliser) in order to maintain the desired biochemical properties or functions of the active component.

It is fully appreciated that in the case of inactivated vaccines, the use of multi-dose containers is discouraged in some member states where the use of single-dose vaccines is perceived to be a fundamentally safer approach. Having said that, there are justifiable cases where the addition of a preservative would enhance microbiological safety of a single-dose product, for example, the production of influenza vaccine utilising eggs as starting materials. It is known that for certain vaccines, the removal of thiomersal is possible without impinging on the stability, immunogenicity and microbiological safety of these products e.g. diphtheria and tetanus toxoid vaccines, some HbsAg vaccines and tick-borne encephalitis vaccine.

2. Are there suitable alternatives to thiomersal available?

Preservatives other than organomercurials have been and are currently used for the preservation of biological products including vaccines: e.g. phenol, cresol, 2-phenoxyethanol and

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formaldehyde. Whilst these preservatives are apparently considered as suitable alternatives to organomercurials, the replacement of this class of preservatives should be carefully considered. All these preservatives fulfil the pharmacopoeia standards. Licensing by national or EU authorities includes favourable evaluation of toxicity and safety and although there are no studies available with respect to toxicology and safety comparing preservative-containing and preservative-free vaccines, the safety/toxicity of these products has been estimated to be acceptable.

In the opinion of the BWP, strict adherence to the principles of GMP will lead or has already led to a situation where preservatives in some biologicals are no longer necessary. Therefore, for certain products, the most desirable alternative may be the encouragement of the development of preservative-free formulations. ?

3. Implications of the removal of thiomersal from medicinal products

Given the fact that there are extenuating circumstances where the use of a preservative is justified on public health grounds, the Biotechnology Working Party considers that the removal of organomercurial compounds in vaccine production has to be assessed on a case-by-case basis taking into account the following:

- Production strategy (see Annex II)
- Vaccines are often turbid which may mask any microbial contamination – the addition of a preservative would suppress any microbial growth

Considerable development and validation work is required to convert a vaccine production process to a organomercurial free one, in such cases a generous strategy for variations should be developed.

In order not to jeopardize vaccine supplies and immunisation programs, it is advisable to introduce requirements for the elimination of organomercurial preservatives in vaccines on a gradual basis. Additional discussions in the appropriate fora may be necessary before any restrictive measures are taken.

Consideration should be given to the fact that organomercurials are no longer used in immunoglobulin preparations and in several biopharmaceuticals.

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ANNEX I

With respect to the rationale for the inclusion/omission of preservatives in biological medicinal products the CPMP adopted during its July 1998 meeting a Guideline on Pharmaceutical and Biological Aspects of Combined Vaccines (CPMP/BWP/477/97). This guideline summarizes the approach to the preservative problem and points out:

"Antimicrobial preservatives should not be included in the finished product unless their use is justified by quality and/or safety considerations. Their use is never acceptable in live vaccines, but may be justified in the case of inactivated vaccines which:

- are present in multi-dose containers and/or
- are presented as suspensions where sterilisation/filtration is impossible.

In all cases where proposals are made that products contain antimicrobial preservatives:

- a benefit risk analysis should be presented in the application dossier; any potential toxicity and/or potential allergenicity should be addressed in this presentation,
- the concentration of the antimicrobial preservatives should be controlled in the bulk and in the finished product specifications in accordance with European Pharmacopoeia limits,
- the efficacy of preservation should be tested according to the Ph.Eur. requirements for human vaccines,
- the maintenance of preservative concentration or efficacy throughout the period of validity should be demonstrated,
- the name and concentration of the antimicrobial preservatives should be stated on the labelling.

In selecting a preservative system the applicant should consider:

- the effectiveness against potential microbial contaminants,
- possible interaction with the formulation or container (for example, thiomersal may be ineffective in the presence of sera and can bind to -SH groups and polymeric material; for toxoid vaccines phenol might impair the antigenicity),
- possible effects on testing in biological systems.

If replacement of preservatives is considered on the basis of side effects or for other reasons, a risk/benefit evaluation should be made, taking into consideration that such a change implies a new formulation with the need for additional studies for sterility, potency, stability and their clinical implications on a case-by-case basis."

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ANNEX II

Special considerations for multi-dose and single-dose parenteral vaccines

Multi-dose parenteral vaccines:

- These require the presence of a preservative to ensure microbial safety during their use while the seal is repeatedly breached over a period of time. This is standard pharmaceutical science. In the case of inactivated parenteral vaccines the use of multidose containers is discouraged in many member states where the use of single-dose vaccines is perceived as a fundamentally safer approach.

Single-dose vaccines:

For monodose containers it seems that there is no quality rationale for adding preservatives to prevent bacterial/fungal contamination during use, since such containers are only sampled once during use. Possible justifications (valid or otherwise) for the inclusion of preservatives in these products are:

- In some vaccines thiomersal is also used during the manufacturing process of the active ingredient itself. In such cases the organomercurial may contribute to the quality of the antigen. A well known example is influenza vaccine which utilises eggs in one of the stages of manufacture, where the addition of thiomersal prevents the vaccine from contamination and from containing unacceptable amounts of endotoxin. Whilst for influenza vaccine the addition of preservatives is imperative, at least in the first stages of production, it has been demonstrated for diphtheria and tetanus toxoid vaccines and with some HBsAg vaccines and with TBE-vaccine, that removal of thiomersal is possible without changes of the microbiological quality (stability, immunogenicity). Therefore the BWP concludes that the possibility of removal of organomercurial compounds in vaccine production has to be evaluated on a case by case basis.
- One final formulated bulk may be used to fill both multidose (where the presence of a preservative is recommended) and single dose containers
- Vaccines are often turbid; thus turbidity could mask growth of a microbial contamination which entered a vial during filling or storage; the presence of a preservative would suppress any microbial growth.
- Vaccines owing to their lability may not be terminally sterilised in their final containers. For vaccines presented as a suspension, the nature of the formulation may preclude them from being sterilised by filtration immediately before filling. The addition of an antimicrobial preservative therefore provides additional assurances with respect to reduction of potential microbial contamination. As a feature of continued research and development, improvements to the manufacturing processes and practices should be encouraged to reduce the need for the inclusion of an antimicrobial preservative.

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The European Agency for the Evaluation of Medicinal Products
Human Medicines Evaluation Unit

CPMP/SWP/1898/1998
8 September, 1998

SAFETY WORKING PARTY

ASSESSMENT OF THE TOXICITY OF THIOMERSAL IN RELATION TO ITS USE IN MEDICINAL PRODUCTS

Rapporteurs: Dr. Jan Willem van der Laan and Dr. Eric de Waal
Co-Rapporteurs: Dr Per Sjöberg and Dr Ulla Liminga

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INTRODUCTION

Thiomersal (Figure 1) is an organomercuric preservative with a MW of 405, of which the mercury component accounts for about 50% (MW 201). Its antimicrobial action is related to the release of ethylmercury, after either spontaneous or enzymatic breakdown of thiomersal into ethylmercury and thiosalicylate. Thiomersal is mainly used in vaccines and immunoglobulins but is also present in other medicinal products, e.g. ophthalmologic products.

The toxicity profile of ethylmercury is very similar to that of methylmercury. Therefore, data on methylmercury are of value for the assessment of risks associated with ethylmercury. In contrast, the toxicological profiles of alkylmercury and of metallic, inorganic mercury are markedly different.

The main causes of concern with thiomersal are the induction of allergic reactions and due to the presence of ethylmercury, the potential risks of neurotoxicity. In non-pregnant adults, a Permissible Total Weekly Intake (PTWI) of 200 µg methylmercury has been recommended by the WHO (1990). At present, there is no international recommendation for a maximal intake by pregnant women or infants. There are considerable human data that indicate a higher sensitivity of fetuses and infants than of adults, due to the vulnerability of the developing brain. Furthermore, owing to the potential for tissue accumulation, administration of even low levels of ethylmercury to pregnant women will add to the overall exposure of infants. Thus, the administration of medicinal products that contain thiomersal as a preservative to pregnant women and to infants may result in an intake of alkylmercury that exceeds the levels that are considered as safe.

The aim of the present report is to assess the potential risks of the use of thiomersal-containing pharmaceuticals, especially vaccines and immunoglobulins. As data for ethylmercury are scarce the report uses the similarity in chemical properties between ethyl- and methylmercury as a starting point. For a more extensive discussion of the risks to human health of methylmercury including data on genotoxicity and carcinogenicity, reference is made to the Environmental Health Criteria 101 on methylmercury issued by the WHO in 1990

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FATE IN THE ORGANISM

Studies on the uptake and distribution of thiomersal in human and animals have shown that it is primarily taken up in the liver and kidneys but also in the brain, skeletal muscles and other organs including skin. In the body, it is mainly converted to ethylmercury and thiosalicylate as is indicated in Figure 1. The thiosalicylate substituent increases the lipophilicity of thiomersal, thereby making the intracellular compartment more susceptible to the ethylmercury residue. Ethylmercury and other alkylmercury compounds have a high affinity for sulfhydryl groups and bind to e.g. proteins or polypeptides in the organism.

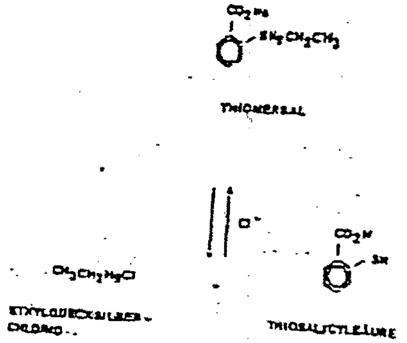

Fig. 1 Structure of thiomersal and its dissociation to form ethylmercury

Distribution. After oral administration of methylmercury, it is distributed to all tissues within 4 days although maximum levels in the brain are only reached after 5-6 days. Concentrations are highest in hair and in a steady-state situation, hair levels may be used to estimate the body burden. In red blood cells, the concentration of methylmercury is about 10-20 times that in plasma, whereas the blood to hair ratio is about 1:250. Also ethylmercury appears to be readily distributed into all tissue compartments in appreciable amounts, including the brain.

Placental transfer of mercury-containing compounds has been studied in animals and humans. Most animal studies with methylmercury clearly show that it may accumulate in the fetus in appreciable amounts, equal or superior to those found in the mother. Studies in various species of rodents have shown that transfer of alkylmercury occurs to a higher degree than that of aryl- or inorganic mercury. Ethylmercury would appear to cross the placenta more easily than methylmercury (Leonard et al, 1983). Studies in rats suggest a peculiar affinity of mercury for the fetal brain, resulting in considerably higher concentrations in fetal than in maternal brain. In humans, as in animals, it is evident that the placenta is very permeable to methylmercury (Leonard et al, 1983).

Distribution studies are not available after intramuscular or subcutaneous administration.

Metobolism and excretion. The gut is the main route of excretion; only small amounts leave the body in the urine. The rate of excretion of mercury in both humans and animals is directly proportional to the simultaneous body burden. Reports are available pointing to an average half-life of 50 days (range 39-70 days) (WHO, 1990). Early data from human and experimental animals indicated that most alkylmercury entering the body was also excreted as alkylmercury (Dales, 1972). However, other data indicate that a substantial part of the methylmercury is converted to inorganic mercury, depending on the organ. For instance, the amount found in faeces was mainly in the form of inorganic mercury (WHO, 1990).

Accumulation. Alkylmercury has a high potential for accumulation in the body at regular intake, even if the individual doses are small. Considerable experience is present from several parts of the world, enabling an approach to calculate a relationship between intake and toxicity and of acceptable levels of exposure. In case of continuous exposure, a single compartment model with a 70-day half-time predicts that the whole-body steady state will be attained within approximately one year and that the maximum amount accumulated will be 100 times the average daily intake (WHO, 1990).

TOXICITY

The main areas of concern relate to induction of sensitisation and neurotoxicity, particularly with respect to the developing brain. The effects of methylmercury in adults differ both quantitatively and qualitatively from those seen after prenatal and possibly also early postnatal exposure. Clinical and epidemiological data indicate that embryo/fetus is more sensitive to the toxic effects of methylmercury than adults. Thus, these populations need to be discussed separately.

The mechanism of toxicologic action of alkylmercury is not completely known, although considerable amounts of data are available. Mercury forms stable mercaptides with proteins containing sulfhydryl groups as well as has affinity for amino-, carbonyl- and hydroxyl groups. The WHO review (1990) indicates that protein synthesis is most sensitive to methylmercury, especially the first stage of synthesis associated with RNA transfer. This leads to a general inhibition of protein synthesis without a selective inhibition of formation of any special proteins or group of proteins.

Thiomersal has a low acute toxicity. The LD$_{50}$ in Fisher rats was in the order of magnitude of 100 mg/kg (Mason et al, 1971). After repeated administration, the toxicity is considerably increased. For instance, in a four-week study in Fisher rats, the maximum tolerated dose was less than 5 mg/kg

Sensitisation

Organic mercury has been found to cause delayed-type hypersensitivity and sensitisation is a well-recognised problem of thiomersal. It is generally considered that the allergic reactions induced by thiomersal is linked to ethylmercury. However, some authors have

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suggested that also the thiosalicylate component may be of importance. Van 't Veen and Van Joost (1994) differentiated 3 groups of patients: (a) positive to thiomersal, but negative to mercurials and thiosalicylic acid; (b) positive to thiomersal and some other mercurials, but negative to thiosalicylic acid; (c) positive to thiomersal and thiosalicylic acid, but negative to other mercurials.

The route of administration also appears to be of importance for the sensitisation potential, where the intra- and epicutaneous routes of administration are associated with a much higher risk for sensitisation than the subcutaneous and intramuscular routes. Förström et al (1980) described 96 patients in Finland with a positive reaction to thiomersal on epicutaneous testing. Twenty percent of 45 thiomersal-sensitive eczema patients developed a reaction after subcutaneous administration of thiomersal (50 μg). It is not fully clear why the incidence was much higher in this study than data referred by Van 't Veen and Van Joost, 1994, where a Tick Borne Encephalitis (TBE) vaccine containing 50 μg thiomersal was given intramuscularly to thiomersal-hypersensitive patients with clinical eczema. In this study, only 2 out of 65 patients developed untoward reactions at the injection site. These differences might be due to the fact that different routes of administration were used. Data from Austria, where a growing number of individuals have been immunised against TBE since 1974, indicate that there is a parallel increase in the number of individuals sensitised to thiomersal (Van 't Veen and Van Joost, 1994)

From earlier data it is suggested that allergic contact eczema induced by thiomersal is rare in Europe. This may be due to its infrequent external use. The frequency of positive epicutaneous test reactions varied from 1.3% in Denmark and the Netherlands to 13.4% in the USA (Förström et al. 1980; Van 't Veen and Van Joost, 1994), which may be related to the fact that a large number of topical OTC products containing thiomersal are available in the USA.

Products containing thiomersal may also cause photohypersensitivity to piroxicam, probably as a result of cross-reactivity between thiosalicylate and a degraded photoproduct of piroxicam. In a study with 2461 patients, 32 (1.3%) had a positive patch test to thiomersal. The highest number of positive reactors fell into the 4th and 5th decades of life.

Neurotoxicity

In cases of alkylmercury poisoning, neural tissue is clearly the target organ of toxicity and the central nervous system is critically sensitive to alkylmercury. The mechanism of this selective damage is not well understood

Data from human subjects and experimental animals suggest that at least two to three weeks (sometimes several months) elapse between the beginning of exposure and the onset of symptoms. The first symptoms are paraesthesia, such as numbness and tingling of fingers, toes, nose and lips; furthermore, slight tremor, headache, fatigue, difficulty in concentration and emotional lability may occur. Mild cases progress no further. For a more detailed description of symptoms for intoxication, see the WHO Review (1990).

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Pre-, peri- and post natal toxicity

Human data on pre-, peri- and post natal toxicity induced by thiomersal alone are limited. In a review published in "Birth Defects and Drugs in Pregnancy" (Heinonen, 1977), an overview of 3,482 children with any malformation in relation to exposure to Topical Antimicrobial Drugs has been presented. Out of 2,918 Mother-Child pairs exposed to antimicrobial agents, 56 pairs were exposed to thiomersal (as ophthalmologic product?) and 6 children showed signs of malformation. Although the number of cases was too small to draw any firm conclusion, the authors concluded that thiomersal was associated with an overall increase of malformations but no rise in specific abnormalities could be identified. No data are available to estimate any measure of exposure.

In contrast to the limited amount of data on thiomersal, there is considerable amount of information on fetal effects of alkylmercury compounds. In the mid-1960s', there was an outbreak of cerebral palsy and microcephaly in newborns from the fishing village of Minimata Bay, Japan (Matsumoto, et al, 1965;). These abnormalities were caused by methylmercury contamination of the fish in the bay. Similar types of intoxication occurred in Iraq after seed grain contaminated with methylmercury was mistakenly used to make bread (Marsh et al, 1980, Amin-Zaki et al, 1976). In this population, infants exposed *in utero* demonstrated psychomotor retardation and cerebral palsy. Similar congenital neurologic disease has been reported in other instances of mercury food contamination.

Experimental animal models of organic mercury embryotoxicity have associated prenatal exposures with a variety of different birth defects, many not seen in human case reports. However, the neurologic effects are generally consistent with the human experience.

Exposure – effect relationships

In the WHO review (1990), data and calculations on exposure-effect relationships for methylmercury were presented. These are summarised in this section.

Data from humans and experimental animals indicate that serious neurotoxicity from alkylmercury commonly occurs at brain concentrations as low as 10 mg/kg, which in humans correspond to a blood mercury concentration of 500 to 1000 µg/L. Blood levels of 100-200 µg/l have not been associated with any symptoms. For reference, 95 % of persons with no known exposure to mercury have blood concentrations below 40 µg/L. Overall, total mercury levels in blood are regarded as a valuable tool for assessing exposure to alkylmercury. A level of 100 µg/l has been proposed as the maximum permissible blood concentration.

The Iraqi data indicated that an intake in adults of 50 µg/day (0.83 µg/kg/d in a 60 kg adult) was associated with a 0.3% risk of developing paresthesia. This is similar to the background frequency of paresthesia and can thus be regarded as a NOAEL (No-Adverse Effect-Level). At an intake of 200 µg/day (3.3 µg/kg/day, 60 kg adult), the risk was about 8 %. A long-term intake of 3-7 µg/kg/d in adults was estimated to cause adverse effects on the nervous system, manifested as an approximately 5% increase in the incidence of paresthesia and can be regarded as a Lowest Observed Adverse Effect

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Level (LOAEL). Such intake would result in blood concentrations of 200-500 μg Hg/l and peak hair concentrations of 50-125 μg/g. Japanese data show that the (first) effects are estimated to occur at levels of 200 μg Hg/l in blood and 80-100 μg Hg/g in hair. It should be pointed out that the background frequency of these non-specific symptoms plays a key role for the accuracy of these estimates. Furthermore, the estimated paresthesia frequency below intakes of about 200 μg/day are extrapolations beyond the observed data and assume the absence of a population threshold.

The WHO (1990) has summarised the data on prenatal exposure as follows:
Severe derangement of the developing central nervous system can be caused by prenatal exposure to methylmercury. In the Iraqi outbreak, the lowest level (maximum maternal hair mercury concentration during pregnancy) at which severe effects were observed was 404 μg/g. The highest no-observed-effect level (NOEL) for severe effects was 399 μg/g. Fish-eating populations in Canada and New-Zealand have also been studied. No severe prenatal effects were seen, but exposure levels were far below the highest NOEL for severe effects in Iraq.

Evidence of psychomotor retardation (delayed achievement of developmental milestones, a history of seizures, abnormal reflexes) was seen in the Iraqi population at maternal hair concentrations well below those associated with severe effects. A statistical analysis revealed that motor retardation rose above the background frequency at maximum maternal hair mercury levels during pregnancy of 10-20 μg/g. This range of concentrations in maternal hair is consistent with all available evidence and can be accepted as the range of critical concentrations. The Canadian study found that maternal hair levels were positively associated with abnormal muscle tone or reflexes in boys, but not in girls (the highest maximum maternal hair level during pregnancy was 23.9 μg/g). The New Zealand study found evidence of developmental retardation in 4-year old children at average maternal hair mercury levels during pregnancy ranging from 6-86 μg/g (the second highest value was 20 μg/g) The New Zealand mercury values should be multiplied by 1.5 to convert them to maximum maternal hair levels in pregnancy.

EXISTING AND SUGGESTED LIMITS FOR INTAKE OF ORGANIC MERCURY

At present, there are no recommendations regarding limits of ethylmercury intake. Due to the similarity between ethylmercury and methylmercury, the recommendations for methylmercury will be presented below. The IPCS report (WHO, 1990) states that the previous recommendation made by the JECFA (Joint Expert Committee on Food Additives) of a permissible tolerable weekly intake (PTWI) of 200 μg methylmercury (0.48 μg/kg/day for an adult of 60 kg) in adults remains. This should be compared with the estimated LOAEL (3.3 μg/kg/d) and NOAEL (0.83 μg/kg/d) for the occurrence of paresthesia (See Section 'Exposure – effect relationships').

With respect to pregnant women, the JECFA considered the available data to be insufficient for the determination of a PTWI. In the WHO report (1990), a maternal hair mercury concentration of 10-20 μg/g was considered critical since the frequency of motor retardation in children began to increase at those levels (based on the Iraq data). When comparing these data with the hair mercury concentrations associated with paresthesia in adults (50-125 μg/g), it appears that adverse effects in children that had been exposed in utero, occurred at about 5 times lower maternal hair levels. In order to

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estimate a reasonably safe intake in pregnant women. it is suggested that the PTWI of 200 µg in non-pregnant adults is reduced by a factor 5. Thus, a weekly intake of 40 µg methylmercury (0.67 µg/kg/week in a 60 kg adult) by a pregnant woman might be considered acceptable to avoid adverse effects in the child (Slooff et al, 1995, RIVM). However, it should be pointed out that there are no data available to set a NOAEL in pregnant women and safety margins can not be established. The figures given above are summarised in Table 1.

Table 1 Summary of limits for intake of organic mercury.

Category	Intake (60 kg adult)	steady state concentration Hg in hair	additional remarks
PTWI (JECFA)	200 µg/week = 3.3µg/kg/week= 0.48 µg/kg/day	Estimated lower limit 7 µg/g	agreed safe level in adults (WHO 1990)
adults (calculated)	50 µg/day		0.3 % paresthesia = NOAEL (proposed)
adults (estimated)	3-7 µg/kg/day*	50-125 µg/g	5 % paresthesia = LOAEL
pregnant women		10-20 µg/g (observed)	motor retardation in children LOAEL
pregnant women PTWI (RIVM)	40 µg/week = 0.67 µg/kg/week 0.095µg/kg/day	Estimated lower limit 1.4 µg/g	estimated safe level

* long-term intake

It is known that the most sensitive developmental symptoms following exposure during pregnancy have a neurological character. Furthermore, the neurological maturation continues several years after birth (Dobbing and Sands, 1973). Thus, it is likely that also young children have a higher sensitivity than adults. If children younger than 1 year are regarded as fetuses, the same limit as for pregnant women could be applied i.e. 0.67 µg/kg/week. If a child (weight at birth 3.5 kg) grows up to 1 year (10 kg), the body burden may initially be approximately 2 µg/week and increase up to approximately 7 µg/week. A total 'allowed' intake for the first year may be estimated to approximately 200-230 µg (26 weeks of 2 µg + 26 weeks of 7 µg).

EXPECTED EXPOSURE

General population

The general population is primarily exposed to methylmercury through the diet. However, air and water, depending upon the level of contamination, can significantly contribute to the daily intake of total mercury. In most foodstuffs, mercury is largely in the organic form and below the limit of detection (20 µg mercury/kg fresh weight). Fish and fish products are the dominant sources of methylmercury in the diet.

WHO estimated that humans have a daily intake of about 2.4 µg methylmercury from all sources, resulting in a daily absorption (95%) of approximately 2.3 µg. The total daily intake of all forms of mercury (including metallic and arylmercury) has been estimated to 6.7 µg, with an addition of 3.8 to 21 µg of mercury vapour from dental amalgams, if present. Intake of mercury-containing fish, even for humans consuming small amounts can markedly affect the total intake of mercury.

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In the WHO report (1990), it was concluded that the general population does not face a significant health risk from methylmercury, although certain groups with a high fish consumption may attain blood methylmercury levels that are associated with an increased risk of neurological adverse effects in adults. Based on that and on an estimation of the normal use of thiomersal-containing medicinal products, it can be concluded that the risk for neurological adverse effects following the use of such products in non-pregnant adults is low.

Young children

In young children, mercury intake via food is difficult to estimate. Based on a 10-fold lower intake than in adults (i.e. 2.3 µg absorbed /day), an intake via food during the first year is estimated to approximately 80-100 µg methylmercury/year. Thus, in relation to the suggested total 'allowed' intake during the first year of 200-230 µg (See Section EXISTING AND SUGGESTED LIMITS FOR INTAKE OF ORGANIC MERCURY), the intake of organic mercury from other sources should not be higher than 120-130 µg during the first year of life.

National Immunisations programs in the European Union (EU) Member States

In Table 2, an overview of the maximum exposure to *ethylmercury* via vaccines containing thiomersal administered during the first and second years of age when using the National Immunisations programs in the European Union (EU) Member States is given. As evident from Table 2, there are large differences between the different National Immunisation programs with respect to the administration of thiomersal-containing vaccines. The highest ethylmercury intake in any Member State during the first 12 months is about 200 µg (240 µg including TBE) and during the first 24 months about 275 µg (300 µg including TBE). Thus, in addition to the estimated intake of about 80-100 µg alkylmercury via other sources such as food (See above), these data indicate that the proposed limit of 200-230 µg/year will be exceeded by about a factor of 2, when applying certain National Immunisation programs.

Table 2: Summary of Maximum Potential Ethylmercury Exposure from thiomersal containing vaccines in National Immunisation Programs in 1st and 2nd year of age

Member State	Up to 1 year of age	Up to 2 years of age (includ. 1st year)
Austria	0.165 mg (0.233 with tick borne encephalitis vaccine)	0.225 mg (0.3 mg with TBE)
Belgium	0.2 mg	0.275 mg
Denmark*	0 mg	0 mg
Finland	0.075 mg	0.1 mg
France	0.188 mg	0.25 mg
Germany	Not calculated	Not calculated
Greece	Not calculated	0.25 mg
Ireland*	0 mg	0 mg
Italy	Not calculated	0.113 mg
Luxembourg	0.063 mg	0.075 mg
Netherlands*	0 mg	0 mg
Portugal	0.075 mg	0.1 mg
Spain	0.3 mg	0.18 mg
Sweden*	0 mg	0 mg
UK	Not calculated	0.15 mg

* There are no vaccines containing thiomersal in these national immunisation programs

Treatment of immunodeficient children

Another risk category is the group of immune deficient children which are treated with immunoglobumin solutions containing thiomersal. Two clinical indications may require the administration of huge amounts of immunoglobulins in infants, i.e. "severe combined immune deficiencies" and "agammaglobulinaemia". The recommended dose of immunoglobulins is 50mg/kg/ week.

In such a case a child of 10 kg may be dosed with 500 mg immunoglobulin. If the concentration is about 16%, then a volume of 3-4 ml/10 kg will be injected on a weekly basis. The concentration of thiomersal in this product can be 0.3 mM, resulting in a dose of 200-260 µg thiomersal/week i.e 100 - 130 µg Hg/week, which is similar in one week to the total permissible yearly intake for mercury in infants below 1 year. (Example taken from the Netherlands).

Pregnant women

Another risk population is clearly pregnant women. In general, vaccinations are not recommended during pregnancy but it may be unavoidable in certain cases. Another source of thiomersal may be the administration of immunoglobulins, e.g. an anti-rubella immunoglobulin in case of a rubella infection which in itself is associated with an increased teratogenic risk. As outlined in Section 'EXISTING AND SUGGESTED LIMITS FOR INTAKE OF ORGANIC MERCURY', intake by a pregnant woman of 40 µg/week may be an acceptable level. However, since these estimations are based on continuous administration, a single administration of 50 - 75 µg ethylmercury via a thiomersal-containing vaccine or immunoglobulin may be acceptable if it occurs only once during pregnancy.

CONCLUSIONS

1. There is ample evidence from the literature that thiomersal may cause sensitisation and subsequent allergic reactions. The implications of this in relation to the use of thiomersal as a preservative in any medicinal product, should be evaluated by appropriate experts.

2. The use of thiomersal in vaccines given to infants in accordance with various national vaccination programs may in certain cases result in approximately 2 times higher intake of ethylmercury during the first year of life than what can be considered as reasonably safe. Given the great uncertainty of the estimations of safe levels in young children, it is suggested to restrict the use of thiomersal in vaccines as a precautionary measure. Since restrictive measures on the use of thiomersal in vaccines within the EU would have wider international consequences, the use of thiomersal as preservative in vaccines may need to be discussed with appropriate international bodies.

3. Various other medicinal products, e.g. immunoglobulins and ophthalmological products, are also preserved with thiomersal. Due to the particular concerns related to the exposure to organic mercury during pregnancy, the use of any thiomersal-containing product in pregnant women should be reconsidered. Furthermore, the use of thiomersal-containing immunoglobulin products in immune deficient children should be avoided.

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Copies of these articles are in most cases available on request.

The European Agency for the Evaluation of Medicinal Products
Human Medicines Evaluation Unit

London, 11 September 1998
CPMP/BWP/1711/98

BIOTECHNOLOGY WORKING PARTY

BWP answer to the questions of the CPMP on Organomercurials as Preservatives in Biopharmaceuticals

The BWP presented a report to the CPMP (CPMP/BWP/1009/97) on thiomersal and other organomercurials as preservative in biopharmaceuticals.

The CPMP prepared a concept paper on thiomersal (CPMP/767/98) in order to enter into discussion with manufacturers with a view to eliminating thiomersal from these products in the future.

From the CPMP the following questions were addressed to the BWP in particular:

1. The rationale for the inclusion of thiomersal in medicinal products

Vaccines consisting of either protein or polysaccharide as active components are usually formulated as a solution or a suspension. These biological matrices as well as different additives can potentially support bacterial and fungal growth. For historic reasons, preservatives including thiomersal have been used in the formulation of biological products such as vaccines in order to minimise potential infections in the recipients which can be fatal. It is well documented in the literature that adventitious microbiological contamination in these products can occur in multi-dose and single-dose presentations which do not include a preservative. This may occur at any stage of the manufacturing process or during use, as a result of repeated broaching of the seal over a period of time. The benefit of including a preservative in the formulation of these products – particularly in multi-dose containers – has been recognised by experts specialising in the development of biological products. There is a general consensus among experts in this field, be they from industry or from Pharmacopoeia, that all biological products presented in multi-dose containers should contain a preservative. The same recommendation has been made for certain single-dose containers for the protection of recipients.

In some instances, a preservative may be added to a product (for example, as a stabiliser) in order to maintain the desired biochemical properties or functions of the active component.

It is fully appreciated that in the case of inactivated vaccines, the use of multi-dose containers is discouraged in some member states where the use of single-dose vaccines is perceived to be a fundamentally safer approach. Having said that, there are justifiable cases where the addition of a preservative would enhance microbiological safety of a single-dose product, for example, the production of influenza vaccine utilising eggs as starting materials. It is known that for certain vaccines, the removal of thiomersal is possible without impinging on the stability, immunogenicity and microbiological safety of these products e.g. diphtheria and tetanus toxoid vaccines, some HbsAg vaccines and tick-borne encephalitis vaccine.

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2. Are there suitable alternatives to thiomersal available?

Preservatives other than organomercurials have been and are currently used for the preservation of biological products including vaccines: e.g. phenol, cresol, 2-phenoxyethanol and formaldehyde. Whilst these preservatives are apparently considered as suitable alternatives to organomercurials, the replacement of this class of preservatives should be carefully considered. All these preservatives fulfil the pharmacopoeia standards. Licensing by national or EU authorities includes favourable evaluation of toxicity and safety and although there are no studies available with respect to toxicology and safety comparing preservative-containing and preservative-free vaccines, the safety/toxicity of these products has been estimated to be acceptable

In the opinion of the BWP, strict adherence to the principles of GMP will lead or has already led to a situation where preservatives in some biologicals are no longer necessary. Therefore, for certain products, the most desirable alternative may be the encouragement of the development of preservative-free formulations.

3. Implications of the removal of thiomersal from medicinal products

Given the fact that there are extenuating circumstances where the use of a preservative is justified on public health grounds, the Biotechnology Working Party considers that the removal of organomercurial compounds in vaccine production has to be assessed on a case-by-case basis taking into account the following:

- Production strategy (see Annex II)
- Vaccines are often turbid which may mask any microbial contamination – the addition of a preservative would suppress any microbial growth

Considerable development and validation work is required to convert a vaccine production process to a organomercurial free one, in such cases a generous strategy for variations should be developed.

In order not to jeopardize vaccine supplies and immunisation programs, it is advisable to introduce requirements for the elimination of organomercurial preservatives in vaccines on a gradual basis. Additional discussions in the appropriate fora may be necessary before any restrictive measures are taken.

Consideration should be given to the fact that organomercurials are no longer used in immunoglobulin preparations and in several biopharmaceuticals.

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ANNEX I

With respect to the rationale for the inclusion/omission of preservatives in biological medicinal products the CPMP adopted during its July 1998 meeting a Guideline on Pharmaceutical and Biological Aspects of Combined Vaccines (CPMP/BWP/477/97). This guideline summarizes the approach to the preservative problem and points out:

"Antimicrobial preservatives should not be included in the finished product unless their use is justified by quality and/or safety considerations. Their use is never acceptable in live vaccines, but may be justified in the case of inactivated vaccines which:

- are present in multi-dose containers and/or
- are presented as suspensions where sterilisation/filtration is impossible.

In all cases where proposals are made that products contain antimicrobial preservatives:

- a benefit risk analysis should be presented in the application dossier; any potential toxicity and/or potential allergenicity should be addressed in this presentation,
- the concentration of the antimicrobial preservatives should be controlled in the bulk and in the finished product specifications in accordance with European Pharmacopoiea limits,
- the efficacy of preservation should be tested according to the Ph.Eur.- requirements for human vaccines,
- the maintenance of preservative concentration or efficacy throughout the period of validity should be demonstrated,
- the name and concentration of the antimicrobial preservatives should be stated on the labelling.

In selecting a preservative system the applicant should consider:

- the effectiveness against potential microbial contaminants,
- possible interaction with the formulation or container (for example, thiomersal may be ineffective in the presence of sera, and can bind to -SH groups and polymeric material; for toxoid vaccines phenol might impair the antigenicity),
- possible effects on testing in biological systems.

If replacement of preservatives is considered on the basis of side effects or for other reasons, a risk/benefit evaluation should be made, taking into consideration that such a change implies a new formulation with the need for additional studies for sterility, potency, stability and their clinical implications on a case-by-case basis."

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ANNEX II

Special considerations for multi-dose and single-dose parenteral vaccines

Multi-dose parenteral vaccines:

- These require the presence of a preservative to ensure microbial safety during their use while the seal is repeatedly broached over a period of time. This is standard pharmaceutical science. In the case of inactivated parenteral vaccines the use of multidose containers is discouraged in many member states where the use of single-dose vaccines is perceived as a fundamentally safer approach.

Single-dose vaccines:

For monodose containers it seems that there is no quality rationale for adding preservatives to prevent bacterial/fungal contamination during use, since such containers are only sampled once during use. Possible justifications (valid or otherwise) for the inclusion of preservatives in these products are:

- In some vaccines thiomersal is also used during the manufacturing process of the active ingredient itself. In such cases the organomercurial may contribute to the quality of the antigen. A well known example is influenza vaccine which utilises eggs in one of the stages of manufacture, where the addition of thiomersal prevents the vaccine from contamination and from containing unacceptable amounts of endotoxin. Whilst for influenza vaccine the addition of preservatives is imperative, at least in the first stages of production, it has been demonstrated for diphtheria and tetanus toxoid vaccines and with some HBsAg vaccines and with TBE-vaccine, that removal of thiomersal is possible without changes of the microbiological quality (stability, immunogenicity). Therefore the BWP concludes that the possibility of removal of organomercurial compounds in vaccine production has to be evaluated on a case by case basis.

- One final formulated bulk may be used to fill both multidose (where the presence of a preservative is recommended) and single dose containers.

- Vaccines are often turbid; this turbidity could mask growth of a microbial contamination which entered a vial during filling or storage; the presence of a preservative would suppress any microbial growth.

- Vaccines owing to their lability may not be terminally sterilised in their final containers. For vaccines presented as a suspension, the nature of the formulation may preclude them from being sterilised by filtration immediately before filling. The addition of an antimicrobial preservative therefore provides additional assurances with respect to reduction of potential microbial contamination. As a feature of continued research and development, improvements to the manufacturing processes and practices should be encouraged to reduce the need for the inclusion of an antimicrobial preservative.

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Annex 3

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Thiomersal: acceptability of a mercury compound in infants and toddlers

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Safety Working Party
CPMP

EXHIBIT

Thiomersal

- ◆ **merfamin**
- ◆ **merseptyl**
- ◆ **merthiolate**
- ◆ **mertogan**
- ◆ **merzonin**
- ◆ **thimerosal**
- ◆ **thiomersalate**
- ◆ **ethylmercurithiosalicylic acid**

Mol.weight:

404.8, mercury 200.6

Thiomersal

- Fate in the organism
- Toxicity
  - sensitization
  - neurotoxicity
  - teratogenicity
- Existing limits for organic mercury
- Expected exposure
  - Exposure in infants
  - Exposure in Pregnant Women

Fate in the organism

Metabolism to thiosalicylate and ethylmercury

Distribution:

- **strong binding to SH groups of proteins**
- **distribution within 4 days**
- **maximal level in brain after 5-6 days**
- **concentration in hair indicative,**
- **ratio blood/hair 1:250**
- **higher penetration through placenta than metallic mercury**

Fate in the organism

- Metabolism
  - metabolism to metallic mercury in de liver, excretion via the feces, around 1% of the body load/day
  - elimination half time 50 days (39-70)
- Cumulation
  - single compartment model with a t1/2 of 50-70 days
  - maximum within a year around 100 x the daily intake

Toxicity, sensitization

- a problem related to the use of eyedrop or ear drop.
- hypersensitivity to:
  - thiomersal , not for mercury and thiosalicylate
  - thiomersal and mercury compounds, notfor thiosalicylate
  - thiomersal and thiosalicylate, not for other mercury compounds
- thiomersal standard in the Patch test of allergologists
- reaction highest with epicutaneous and intracutaneous administration, less with subcutaneous and intramuscular administration.
- Positive epicutaneous tests:
  - 1,3 % in Danmark and the Netherlands
  - 13,4 % in US (more OTC products with thiomersal)
- vaccins will be administered intramuscularly, therefore at less risk.

Toxicity of thiomersal

Presumption:

Ethylmercury exhibits a similar toxicity profile as methylmercury

A lot is known about methylmercury (exposure, toxicity) which will be extrapolated to ethylmercury.

Toxicity, neurotoxicity

Long-term toxicity derived from environmental accidents and fish eating populations:

- **Iraqi grainpoisoning** (1970's)
- **Minimata bay**
- **Swedish and Canadian fishconsumption**

Mechanism:

- **binding to proteins, sulfhydryl, amino, carboxyl and hydroxyl groups**
- **protein synthesis most sensitive to alkylmercury**
- **selective damage of CNS not fully understood.**

Toxicity, neurotoxicity

Symptoms

- **paresthesia, tingling of fingers, toes, nose and lips**
- **light tremors, headache, fatigue, difficulty to concentrate, emotional lability** higher concentrations

Concentration related:

- **serious toxicity: brainconcentration 10 mg/kg, blood Hg concentration 0,5-1,0 mg/l**
- **no-effect level: 0.1-0.2 mg Hg/l blood. (0.1 mg/l maximal allowed concentration**

Based on Iraqi outbreak of 1970s

Toxicity, neurotoxicity

- Dose-response relations based on Iraqi outbreak 1971-1972
- Consumption of seed grain, treated with methylmercury
- Total 6000 victims with 400 deaths
- Individual exposure varied between low (one day) to long-term (2 months daily intake)
- Dose-response relations as calculated in 1976

Toxicity, neurotoxicity

- **Recalculation by Nordberg and Strangert, 1982**
  - **daily intake of 50 ug induces risk of 0.3% paresthesia**
  - **daily intake of 200 ug induces a risk of 8%**
- **What is the backgorund frequency of paresthesia? Estimation is 6.3% but the reliability is low**
- **WHO: Lowest limit accepted as 5%, with a daily intake of 3-7 ug/kg body weight. This intake will result in 200 ug Hg/l in blood and in hair 50 ug/g**

Toxicity, neurotoxicity

- **Evidence from fish-eating populations**
- **Canada**
  - **Wheatly 1979: 84 persons >100 ug/l in blood, in 11 cases a relation could not be excluded**
  - **McKeown, 1983: degree of the effects moderate to low at concentrations of 600 ug/l in blood**
- **Japan:**
  - **Various authors: No effect at 200 ug/l in blood. Consistent with paresthesia incidence of 3%.**

Toxicity, teratogenicity

Prenatal exposure

Minimata

- 23 children in utero exposure with cerebral palsy and psychomotor retardation, with mothers with no or low symptomatology
- studies on influence on IQ not consistent, possibly because of lack of data of exposure of the mothers

Iraq

- Marsh, 1981: 84 mother/child pairs with concentrations in hair of 0.4-640 mg/kg. Serious neurological symptoms in 5 children. Most sensitive the children exposed to methylmercury in the 4th and 5th month of pregnancy. Mothers show paresthia only.

Toxicity, teratogenicity

- **Relation between concentration in mother hair and cases of psychomotor retardation**

Toxicity, teratogenicity

Hockeystick model

Toxicity, teratogenicity

tabel 10

Toxicity, teratogenicity

- Risk calculation based on threshold approach
- Lowest concentration with serious effect: 404 ug/g in hair
- no effect level
  highest NOEL: 399 ug/g in hair
- fish-eating populations do not reach this level and do not contribute to the risk estimations
- Increase above background level from 10-20 ug/g in hair.

Expected exposure

Sources

- Food, mostly fish
- amalgam fillings
- other exposure (a.o. vaccins)

Estimated intake

methylmercury 2.4 ug/day with 90 % absorption, thus 2.3 ug/day

other mercury 6.7 ug/day with 3.8-21 ug if amalgam is present

Dail consumption of fish leads to a considerable exposure of methylmercury, even with small quantities (10-20 g/day)

JECFA (1989): Provisional Tolerable Weekly Intake (PTWI) 200 ug

Safety Margin

- 50 ug/day (0.71 ug/kg body weight, in a 70 kg adult) induces 0.3% paresthesia (= backgroundfrequency)
- 200 ug/day induces 8% paresthesia

If 5% is taken as the LOAEL then the daily intake is 3-7 ug/kg body weight with concentrations of 200-500 ug Hg/l in blood and a hair concentration of 50-125 ug/l

The PTWI of 200 ug/week = 0.4 ug/kg/day for an adult, results in a safety margin of 7 compared with the LOAEL.

Safety Margin in pregnant women

- **JECFA: Available data are insufficient**
- **WHO 1990: Critical range 10 -20 ug in hair of mothers (in fact LOAEL)**

(lowest observed effective level)

The LOAEL is a factor 5 lower than for adults (critical range is 50-125 ug/g in hair) (RIVM, Slooff et al 1995)

40 ug/week appears to be a safe level, but no safety margin is present

Summary:
limits for organic mercury

Safety margin in infants < 1 year

Infants are vaccinated in their first year. Are infants similar to adults or similar to fetuses (i.e. with a 5 times higher sensitivity)

Organic mercury is mainly toxic to the Central Nervous System

Brain development is independent of birth. The sensitivity of infants should be set at the higher sensitivity, i.e. with a limit of 0.57 ug/kg body weight/week.

A child (birth weight 3.5 kg) is growing in a year to 10 kg. The intake might be for the first half year of 2 ug/week and for the second half 5.7 ug/week. In total 200 ug for the first year of life.

Intake via the food is estimated as 80 ug methylHg/year

Estimate of 375 µg during first 12 months from vaccines

Safe intake can be 120 ug/year

Conclusions

To the CPMP it is recommended

◆ Sensitization caused by thiomersal might be caused by local administration of non-biologic preparations. Direct removal of thiomersal is not necessary.

◆ Toxicity is especially a problem because of the high number of vaccinations in the first year. In vaccins thiomersal should be replaced by another preservative, e.g. phenoxyethanol. This should be discussed with the appropriate international bodies.

◆ Various other products such as immunoglobulins and eye drops contain thiomersal. Administration to infants or to pregnant women may result in toxic exposure.

CBER/OVRR Review under FDAMA Section 413(c)

Table 4 - Exposure to Mercury from Vaccines in U.S. Infants (≤ 6 months)

Vaccine	**Minimum Mercury Dose**	**Maximum Mercury Dose**
DTaP x 3	0 µg	75 µg
Hib x 3	0 µg	75 µg
Hepatitis B x 3	0 µg	37.5 µg
Hib-Hepatitis B x 2	0 µg	NA
[Influenza][ξ] (selected populations)	[12.5 µg]	[12.5 µg]
Total	**[12.5 µg]**	**187.5 µg [200 µg]**

[ξ] Brackets denote dose of mercury if influenza vaccine is administered.

Thimerosal is 49.6% mercury by weight; e.g., 0.005% thimerosal concentration is equivalent to 50 µg thimerosal/1.0 ml or 25 µg thimerosal/0.5 ml and results in approximately 12.5 µg mercury/0.5 ml dose

Note: These calculations do not include mercury exposures from sources other than vaccines.

NA: Not applicable

PENGAD-Bayonne, N.J.
EXHIBIT
7

Table 3: Calculated Exposure Limits for Mercury, Using Various Agency Guidelines for Exposure to Methylmercury, in Infants ≤ 6 Months of Age by Percentile Body Weight

Agency	**Percentile Body Weight**		
	5th	**50th**	**95th**
EPA	65 µg	89 µg	106 µg
ATSDR	194 µg	266 µg	319 µg
FDA	259 µg	354 µg	425 µg
WHO	305 µg	417 µg	501 µg

- Calculated Exposure Limit = dose/kg body weight/week X average weight X 26 weeks X 0.932 (mercury molecular weight/ methylmercury molecular weight); e.g., EPA calculated exposure limit = 0.7 µg/kg body weight/week X 26 weeks X (2.36 kg + 5.25 kg)/2 X 0.932 = 65 µg.
- Assumes average of 5th, 50th, and 95th% weight for females at birth (2.36 kg, 3.23 kg, 3.81 kg) and 6 months (5.25 kg, 7.21 kg, 8.73 kg) = 3.81 kg, 5.22 kg, 6.27 kg. Females were selected because their smaller body weight makes them more susceptible than males.
- Recommended limits on methylmercury exposure:

  EPA: 0.1 µg/kg body weight/day; ATSDR: 0.3 µg/kg body weight/day;

  FDA: 0.4 µg/kg body weight/day; WHO 3.3 µg/kg body weight/week.

  For calculations, daily limits multiplied by 7 to obtain weekly limits.

EXHIBIT
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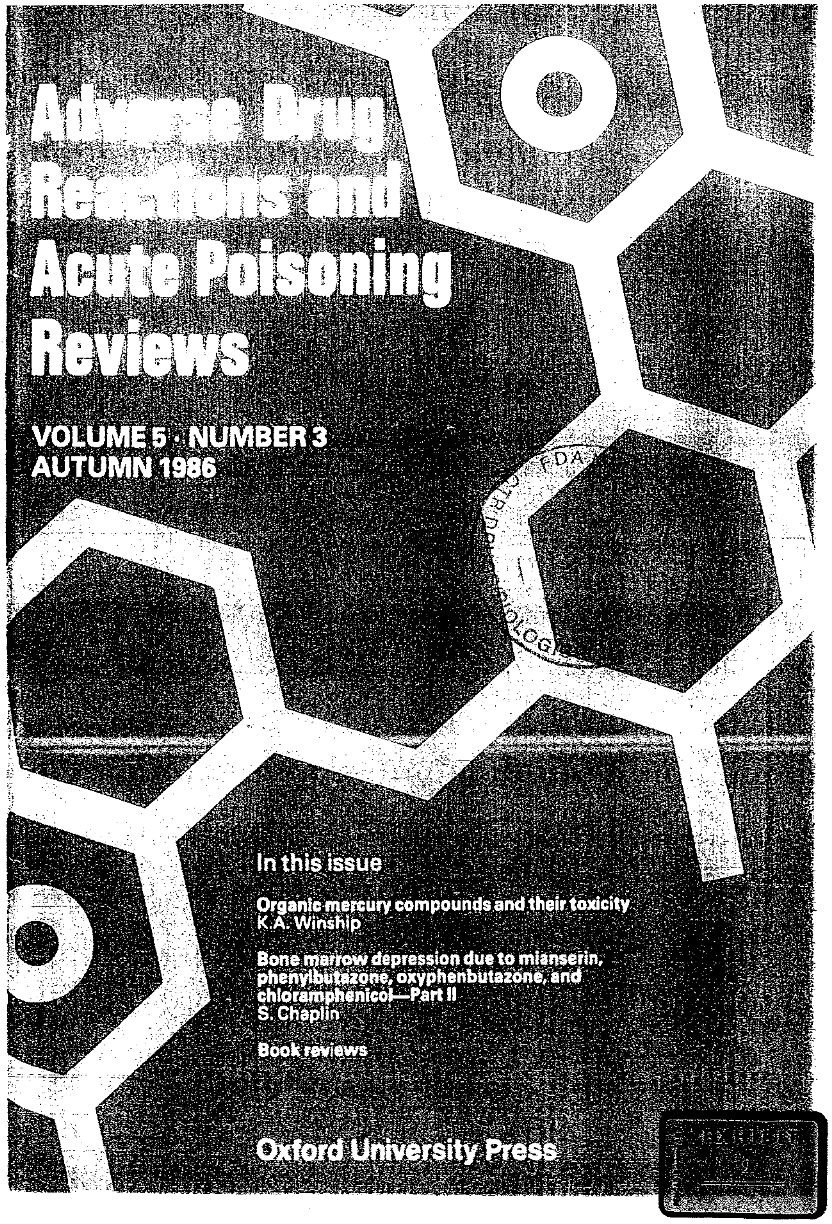

Adverse Drug Reactions and Acute Poisoning Reviews

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In this issue

Organic mercury compounds and their toxicity
K.A. Winship

Bone marrow depression due to mianserin, phenylbutazone, oxyphenbutazone, and chloramphenicol—Part II
S. Chaplin

Book reviews

Oxford University Press

EXHIBIT

Uses

Present day medicinal employment of organic mercury compounds is chiefly limited to their use as antiseptics and preservatives. They have been marketed in various types of proprietary solutions, tinctures, jellies, ointments, and suppositories.[7] Because organic mercurials are less irritating than soluble inorganic mercurial salts they can be applied directly to tissue. Mercurochrome was the first organic mercurial antiseptic to be introduced. The other organic mercurial antiseptics are phenylmercuric acetate (PMA), phenylmercuric nitrate (PMN), phenylmercuric borate, and thiomersal. The main group of products containing these preservatives is ophthalmic products, such as eye drops, eye lotions, and contact lens solutions. They are also contained in vaccines, antigens, and immunoglobulins, and to a lesser extent they have also been used in nasal drops and sprays, injections, lyophilized powders, and creams. ✳

Apart from their use in pharmaceutical and cosmetic preparations, phenyl, ethyl, and methyl compounds (especially PMA, ethyl mercuric chloride, methyl mercuric iodide) are used in the manufacture of liquid and powder seed dressings; as steeps and dips to inhibit the growth of fungi and to delay germination,[9] in the cultivation of wheat, oats, other cereals, sugar beet, seed potatoes, and cotton; and for controlling apple and pear scab. Other organic mercury compounds are also used to control slime in the cellulose and paper industry.

Clinical manifestations of poisoning by organic mercury compounds

Acute poisoning

Acute poisoning may be caused by organic mercury compounds but less commonly than from oral ingestion of inorganic preparations. Systemic effects commence within a few hours and may last for days. Nausea and vomiting occur, accompanied by severe abdominal pain which may be made worse by the vomiting. If the poison reaches the small intestine, severe haemorrhagic diarrhoea follows, with profound shock and possibly death.[7] If the colon is affected, diarrhoea may aggravate protein and fluid loss. In organic mercury poisoning, as with inhalation of mercury vapour, lethargy or restlessness, fever, pneumonitis with tachypnoea, cough, chest pain, and cyanosis occur, often followed by atelectasis, emphysema, haemoptysis, and pneumothorax. Phenylmercuric compounds, like inorganic salts, act on capillary epithelium, specifically in the kidney, colon, and mouth. If renal damage is extensive, oliguria and eventually anuria result. Both ethyl and MeHg compounds, like elemental mercury, can also cause excitement, hyperreflexia, and tremor.

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Chronic poisoning

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General considerations

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Very rarely after intravenous administration of an organic mercurial diuretic a fatal reaction has occurred due to ventricular fibrillation produced by a transient high concentration of the drug.[10]

Chronic poisoning

The most consistent and pronounced effects of short-chain alkyl mercury compounds, such as MeHg, are on the central nervous system; these are similar to those caused by mercury vapour and are both neurological and psychiatric. Typically, symptoms include depression, irritability, exaggerated response to stimulation, excessive shyness, insomnia, emotional instability, forgetfulness, confusion, and vasomotor disturbances such as excessive perspiration and uncontrolled blushing. Intention tremor develops and is reversible.[11] Fine trembling of the fingers, eyelids, lips, and tongue may be interrupted intermittently by coarse shaking movements. Sensory signs are characteristic of MeHg exposure, the earliest sign of which is paraesthesia; this occurs in the tongue and lips and somewhat later in the fingers and toes.[12] At higher levels of exposure, ataxia, dysarthria, constriction of the visual fields, and hearing defects develop. These signs were considered to be irreversible at first, but further experience has shown that improvement can occur even though progress may be slow. The neuropsychiatric effects are not marked, as occurs with mercury vapour, but are more likely to involve spontaneous fits of laughing and crying and also intellectual deterioration.[7] In 1940 four cases were reported[13] of poisoning by inhalation of MeHg compounds in a factory where fungicidal dusts were manufactured without the use of enclosed apparatus. Apart from tremor, symptoms of inorganic mercury poisoning were absent. Only the nervous system was affected and all cases demonstrated severe generalized ataxia, dysarthria, and gross constriction of visual fields, while memory and intelligence were unaffected. One of these men was still disabled 30 years after exposure. Further cases reported in the 1940s and 1950s were also related to occupational exposure.[12,14,15]

General considerations

Sources of organic mercury exposure

Exposure to organic mercury has mainly followed environmental pollution, due to increased industrial use of mercury. Atmospheric contamination occurs following the burning of coal and other fossil fuels, the residues being washed down by rain and deposited on surface soils and water.[16] Vapour and dust which result from the mining, refining and smelting of mercury also release mercury to the atmosphere. Effluents from chloralkali plants, which use mercury as a cathode, have polluted water. Extensive use has been made of organic mercury compounds as antifungal agents, such as seed dressings in agriculture and slimicides in the pulp and paper industry.[9] Mercury is also released to the environment as the result of its various uses: as a mildew preventative in paints, as a catalyst in chemical manufacture; in dental preparations and pharmaceuticals, and as components of electronic and physical measurement devices, including thermometers. Through natural processes much of the mercury in and on soils eventually reaches rivers, lakes, and seas, and settles in these marine environments. There, a number of aquatic microorganisms can methylate inorganic mercury,[17] and the resulting compound is taken up by fish which, if eaten in large enough quantities, causes poisoning, as occurred in Minamata and Niigata in Japan. Another source of MeHg exposure is fungicide, particularly that used in treating grain. When treated seed is planted, the crops that grow do not contain dangerous amounts of mercury. Treated seed may, however, be eaten in error as occurred in reported epidemics in Ghana,[16] Iraq,[18] Pakistan,[19] Guatemala,[20] and the Soviet Union.[21]

Chemical forms of organic mercury compounds

There are three types of organic mercurials: these are alkyl salts, for example CH_3Hg^+ and aryl salts $C_6H_5Hg^+$, and a special group of alkyl mercurials which are the mercurial diuretics.

In general, the organic mercurials are less soluble in aqueous media than are the inorganic mercurials; but they are much more soluble in lipids than the mercuric salts or complexes. Although the affinity of the mercurous ion for many ligands is less than is that of the mercuric ion, the reactivity of both forms of mercurials with SH groups is greatly reduced by the presence of Cl^-, OH^-, and amino acids or other sources of nitrogen ligands; and the weakness of the carbon–mercury bond of the organic mercurials is of importance in understanding the movement and distribution of Hg^{++} in biological tissues when one of the former has been administered. The mercurial diuretics are less reactive with tissues other than the kidney.[22] The physical properties, that is, solubility and volatility, of phenyl mercury and methoxyethyl mercury compounds make them more easily absorbable than inorganic salts. The aryl organic mercurials behave more like the inorganic compounds.

Methods of detection and analysis

Many analytical techniques are available for the detection and measurement of mercury, depending on the quantity to be analysed and the chemical nature of the sample; some methods are briefly described below.

Classical methods

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GAS CHROMATOGRAPHY

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Classical methods

COMPLEXIOMETRIC METHOD

Dithizone was the most frequently used colorimetric reagent for the measurement of mercury compounds in the 1950s and 1960s. The procedure makes use of wet oxidation of the sample followed by extraction of mercury in an organic solvent as a dithizonate complex and finally the colorimetric determination of the complex itself. Selectivity for mercury is obtained by adjusting the conditions of the extraction. This method has a sensitivity of about 0.5 μg of mercury.[23]

TITRIMETRIC METHODS

Inorganic mercury compounds can be titrated directly using EDTA with hexamine as a buffer and xylenol orange or methylthymol blue as indicators.[24] Mercury can also be determined by precipitating the mercury as mercurous chloride and, after reacting the precipitate with concentrated hydrochloric acid, water, and carbon tetrachloride or chloroform, titrating with standard 0.1N potassium iodate solution.[24]

Chromatography

LIQUID-SOLID CHROMATOGRAPHY

A method of separating inorganic and organic mercury, on an alumina column after extraction with dithizone, has been developed.[25] This method allows inorganic and organic mercury to be separately determined at levels to 0.02 parts per million(ppm).

GAS CHROMATOGRAPHY

Inorganic mercury in biological materials can be measured by isolating it as MeHg after reaction with tetramethyl tin. Total mercury recovery ranges between 75 and 90 per cent and is assessed by using appropriate ^{203}Hg-labelled compounds for liquid scintillation spectrometric assay. Specific gas chromatographic conditions allow detection of mercury concentrations of 1 ppb or lower.[26]

HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

HPLC is one of the more recent techniques used for the determination of small amounts of organic mercury compounds. It is advantageous for the separation of organic mercury compounds because even unstable samples are not decomposed and so can be determined quantitatively. Using an atomic absorption spectrophotometer and eluent vaporizing system, a higher sensitivity is achieved.[27] A rapid and sensitive method for the determination of PMN was developed[28] using a silica gel column with hexane/ethanol as the mobile phase. The detection limit was about 1.5×10^{-3}g per l. The method is applicable to eye-drops. There are also methods for determining thiomersal using HPLC.[29,30] Radial compression separation has been validated for the determination of thiomersal,[31] with excellent resolution and analysis times. The detection limit is estimated to be 0.13 ppm. HPLC is reliable, rapid, and sensitive but it is somewhat more expensive than the complexiometric and titration methods.[32]

ELECTROPHORESIS

High-voltage agar gel electrophoresis is a method described[33] for the separation and microbiological detection of preservatives in pharmaceutical and cosmetic products. PMA, PMN, and thiomersal can be detected in low concentrations. This method is very slow but fairly cheap.[32]

Spectroscopy

ABSORPTION SPECTROSCOPY

Spectrophotometry is used as the final step in many analytical methods.

ATOMIC ABSORPTION SPECTROMETRY

Many atomic absorption spectrometry techniques used for the determination of mercury are based on the method described by Hatch and Ott[34] in which mercury can be measured down to one part per billion (ppb) in solution. The procedure involves oxidative digestion and wet-ashing, followed by reduction, aeration, and measurement of the mercury-vapour absorption, through the quartz cell of an atomic absorption spectrometer. The procedure is free from interference by organic matter or other volatile constituents of the sample. This method is popular, fast, sensitive, and very accurate. Its detection limit is 1 ppb. A flameless atomic-absorption spectrometry technique for measuring mercury in fish homogenates[35] has also been described for PMN in pharmaceutical preparations.[36] The method is rapid and sensitive and there is no matrix interference. Other cold vapour techniques to assay organic compounds in vaccines used in veterinary medcine[37] and in vaccines and globulins[38] are also available.

Radiochemical methods

ACTIVATION ANALYSIS

There are two forms of this method, the radiochemical separation form and the purely instrumental form. Neutron activation analysis involves placing a known amount of sample into a container and subjecting it to neutron bombardment along with a mercury reference material. The induced radioactivity of ^{197}Hg and ^{203}Hg is the basis of this method.[39] It is a reliable, efficient, and highly specific method, with a detection limit of 0.5 μg

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Electrometric methods

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per g; it has no reagent blank and is independent of the chemical form of the element. The disadvantages are that it is slow, expensive, and cannot be adapted for field use, because special radiation facilities and data processing are required. The method measures total mercury; consequently, to differentiate organic mercury compounds from inorganic salts or from the elemental form a suitable solubility test in an organic solvent is a simple and adequate complement.

TRACER ANALYSIS

This method involves the use of a tagged phenylmercuric salt and is useful for monitoring the behaviour of preservatives during storage but it is not suitable for routine analyses.

ISOTOPE EXCHANGE

This method also involves the use of a tagged phenylmercuric salt for routine analysis but is expensive and less rapid than other methods described.

Electrometric methods

POTENTIOMETRIC TITRATIONS

A simple assay has been developed,[40] for the measurement of small amounts of mercury salts in aqueous solutions in which the end point is detected potentiometrically using an electrode sensitive to iodine ions. The technique is rapid, sensitive, and cheap and can detect concentrations of less than 1 ppm. Some active drug substances, however, may interfere.

POLAROGRAPHY

Many authors have shown that mercurous and mercuric ions yield well-defined diffusion currents that are directly proportional to the concentration of the mercurous or mercuric salt.[32]

AMPEROMETRIC TITRATIONS

COULOMETRY

These methods are not widely used.

Microbiological assay

Microbiological assays are useful for measuring the antimicrobial activity of the organic mercurial preservative in biological products such as vaccines.[33]

Pharmacology and Pharmacokinetics

The absorption, distribution, and excretion of mercury in organic compounds is dependent on the physicochemical characteristics and the extent of *in vivo* conversion to inorganic mercury.

Absorption

Organic mercury compounds are absorbed more completely from the gastrointestinal tract than are the inorganic salts, because they are more lipid-soluble and less corrosive to the intestinal mucosa.[7] Between 90 and 100 per cent of MeHg compounds is absorbed from the gastrointestinal tract,[7,41–3] whereas absorption of phenyl mercury, like inorganic compounds, is considerably lower.[16] Organic mercury compounds present in vaginal jellies are easily absorbed and retained in the body.[44] Fungicidal organic mercury ointments have led to percutaneous absorption, but adverse effects may be partly due to inhalation, as alkyl compounds are volatile.

Distribution

Organic mercurials are distributed more evenly and widely throughout the body than are the inorganic salts,[7] but as they undergo biotransformation, with splitting of the carbon–mercury bond and release of inorganic mercury, their distribution pattern becomes similar to that shown by the inorganic mercury compounds. In a comparative study,[45] it was shown that the toxicities of organic compounds were directly related to their rate of breakdown to yield inorganic mercury, therefore suggesting that inorganic mercury was the toxic agent. Initially, the liver and kidney have the highest concentrations of mercury, with about 50 per cent of the body content in the liver.[43] In the liver mercury is contained in lysosomes/peroxysomes.[46] It is then concentrated in the blood, brain, hair, and epidermis.[42,47] Of the amount present in the body a significant portion is in the blood,[48] where 90 per cent enters the red blood cells and its concentration in them is about five times higher than in plasma [49] (which is in contrast to around 50 per cent following exposure to inorganic mercury). Red cell analysis for MeHg is, therefore, a reliable diagnostic index of absorption. The amount in plasma is bound to albumin,[50–3] and there is evidence suggesting that it is bound to glutathione in red cells.[54] Normal blood levels of mercury are generally below 1 μg per 100 ml, the upper limit being about 3 μg 100 ml. MeHg is deposited in hair, the hair:blood ratio being about 280:1.[55] In an unexposed population of city dwellers the range of mercury concentration in hair was found to be 0.16 to 1.02 μg per g,[56] which is lower than the normally quoted range of 0.3 to 4.0 μg and lower than 10 μg per g which was stated previously to be the normal human level.[57] In general, hair concentrations over 150μg per g (150 ppm) are associated with toxicity.[58] The uptake into the brain is delayed,[59] and after chronic exposure about 10 to 15 per cent may be localized in the brain; more recent findings suggest that 3 to 7 per cent of the total body burden accumulates in the brain.[60] Investigations in monkeys showed
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gations in monkeys showed that the brain to blood ratio is dose-dependent and at high blood mercury levels the brain levels are disproportionately higher.[61,62] The highest uptake in the nervous system is in the sensory ganglia; organic mercury is more selective for neurones than for glia and other satellite cells.[63] When the Minamata autopsy samples were analysed by electron microscopy methods, mercury particles 10 μm or less in size were located in the cytoplasm of nerve cells, astrocytes, and endothelial cells.[64]

In contrast to inorganic or phenyl mercury compounds, MeHg compounds pass through the placental barrier readily and can accumulate in the fetus.[65] The average mercury concentration of fetal erythrocytes is about 30 per cent greater than maternal values. Differences in haemoglobin composition favour the accumulation of MeHg in fetal blood and, therefore, the fetus is more susceptible than the mother to poisoning.[66] In man, the brain mercury concentration appears to be dose-dependent; the fetuses of women with average mercury exposure have been found to have brain concentrations not significantly different from those of average adults, which indicates that under ordinary circumstances the fetal brain is not exposed to mercury levels greater than adult values.[67] Detailed investigation[49] of mothers and their infants showed that MeHg is transferred into milk, which was shown to contain 5 to 6 per cent of the mercury concentration of maternal blood. Continued ingestion of breast milk for a period of months or years was shown to lead to substantial levels in the suckling infant in the outbreak in Iraq.

Biotransformation

MeHg has been shown to be converted to inorganic mercury experimentally, by cleavage of the carbon–mercury bond. This has also been confirmed in human tissues. The rate of conversion is less than one per cent per day and accounts for the presence of inorganic mercury in the body after dietary intake of MeHg. Raised levels of inorganic mercury as well as MeHg in hair were noted in the Iraq outbreak, where exposure was exclusively from MeHg.[49] Biotransformation of organic mercury was studied in the rat[68] using ^{203}Hg-labelled methyl mercury chloride and measuring the amount of organic and inorganic mercury in the brain, liver, kidney, red blood cells, and plasma. Mercury in the blood was almost totally bound in the red blood cells, and the blood:plasma ratio of about 300 did not change significantly over the period of 50 days of testing. Inorganic mercury was detected in plasma, brain, and organs involved in excretion. The inorganic mercury form is redistributed in organs, as occurs following injection of inorganic mercuric salts; biotransformation is therefore important in the excretion of mercury following exposure to an organic compound. The delay in the appearance of the central nervous system effects could not be explained by the accumulation of inorganic mercury in brain tissue, as this fraction was in the range of 1–4 per cent and practically all the mercury in brain was in the organic form. The uptake and release of mercury by brain tissue was much slower compared with changes in blood levels. The brain level did not reach its peak until the sixth day and fell only by 25 per cent in the following 10 days, whereas the levels in the blood and plasma fell by 55 per cent and 45 per cent respectively. The maximum renal levels of organic mercury occurred on the second day and fell by about 50 per cent from the second to the tenth day, as did the levels in whole blood and plasma. The amount of inorganic mercury gradually increased to a maximum level on the 30th day when it accounted for about 90 per cent of mercury in the kidney.

Excretion

When mercury transport pathways through the gastrointestinal tract were investigated after exposure to ^{203}Hg-labelled MeHg salts in rats,[69] mercury was excreted in bile mainly as methyl mercury cysteine, and was rapidly reabsorbed. Some MeHg has been found in a complex with glutathione in the cytosol and in the bile. Recently, *in vitro* conversion of methyl mercury glutathione to methyl mercury cysteine by bile enzymes has been demonstrated.[70] Shed intestinal cells are the main faecal mercury source; these cells, however, contain less inorganic mercury than the amount in faeces. MeHg bound to structural proteins in these cells releases inorganic mercury formed by lower intestinal microbiological action. Biliary excretion is increased by phenobarbitone.[71] Elimination of organic mercury compounds from the body is slow but accelerates during the first 30 days after exposure.[43] Excretion is mainly through the faeces; less than 10 per cent of a dose appears in the urine. Although MeHg is excreted mainly through bile into the intestine, it is almost immediately reabsorbed into the blood[69] and it is this process that partly accounts for its lengthy presence in the body. It can, therefore, accumulate in the body in proportion to dietary intake as has been demonstrated by measuring blood mercury levels in fish-eating populations in Sweden. The biological half-life has been shown to be about 70 days in human volunteers; this corresponds to an excretion rate of about one per cent per day of the total body burden.[42,49] The accumulation of the organic mercury compound in the red blood cells effectively traps it in a form not available for excretion. The slow rate of metabolism does not allow the organic compound to be converted to a form where the red blood cell:plasma ratio would allow more rapid excretion. In contrast, aryl compounds of mercury also accumulate in the red cells but they are rapidly converted to inorganic mercury with corresponding changes in red blood cell:plasma ratio.[47] As a result the body burden of mercury declines much more rapidly than after exposure to MeHg compounds. The upper limit for excretion of mercury in urine is 25 μg per l, but it is not a reliable indicator of blood MeHg levels.[49]

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Toxicology

Experimental toxicology

Acute studies

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Action and toxicity of mercurial diuretics

At the time when organic mercurial diuretics were introduced it was thought that diuretic effect was by the release of inorganic mercury in the kidney. The so-called 'mercuric ion' hypothesis received strong but direct support from studies in dogs.[72] Clarkson and colleagues[73] demonstrated in the rat that renal levels of mercuric ion correlated with the onset of diuresis. This basis for action of organic mercurial diuretics was also accepted by Kazantzis[74] in his review of the effect of mercury on the kidney. The mechanism involves concentration within the kidney and release of small amounts of mercuric ions in the proximal tubular cells which, dependent on intracellular pH, depress reabsorption of sodium and chloride and excretion of potassium. These compounds are acid-labile to facilitate rupture of the carbon–mercury bond. The advantage of organic mercurials over inorganic compounds is that they are rapidly excreted by the kidney. They can therefore produce reversible functional changes in the renal tubule with minimal danger of producing pathological lesions in the kidney or elsewhere in the body.[10] About 50 per cent of injected mercury can be recovered in the urine within 3 hours and up to 95 per cent within 24 hours; therefore very little appears in the bowel. Excretion is retarded in individuals with impaired renal function.[10]

Toxicology

Experimental toxicology

Acute studies

The LD_{50} lies between about 10 and 40 mg per kg body weight for all compounds tested, including inorganic mercury, arylmercury, alkoxyalkyl, and alkylmercury compounds.[75] The LD_{50} of the different types of mercury compounds when given in acute massive doses are similar because mercury in any chemical form will denature proteins, inactivate enzymes, and cause severe disruption of any tissue with which it comes into contact in sufficient concentration. The signs of acute toxicity usually consist of shock, cardiovascular collapse, acute renal failure, and severe gastrointestinal damage.[75]

Subacute and chronic studies

PMA when fed to rats for long periods resulted in renal changes similar to those of mercuric chloride because phenyl mercury compounds are rapidly converted to inorganic mercury in animal tissues.

Doses of alkylmercury compounds insufficient to cause neurological signs, caused a decrease in rat liver mixed-function oxidase activity, due to increased degradation rate of cytochrome P-450 *in vivo*. MeHg also depressed the activity of enzymes dependent upon cytochrome P-450.[76] In rats, MeHg can produce kidney damage, shown by tubular degeneration in the distal convoluted tubules after daily dosing for one week.[77] With lower doses, functional renal damage occurred without signs of neurological dysfunction. It was suggested that the renal effects were due to inorganic mercury formed from MeHg *in vivo*.[78] In animal studies, the neurological effects were shown to be sensory and of wide distribution when the animals were exposed to methyl mercury iodide and methyl mercury nitrate.[13] The effects were similar whether the compound was given by ingestion or by inhalation. There was a latent period between exposure and the development of neurological symptoms in rats and the monkey. The symptoms were principally severe ataxia with loss of position sense and muscular co-ordination. The monkey received comparatively much smaller doses than rats, suggesting that primates may be more susceptible to organic mercury compounds (in rats the peripheral nerves and posterior spinal roots were affected first, and the posterior columns and the granular layer of the middle lobe of the cerebellum later).

Further studies[79] have shown sudden visual disturbance in monkeys given low doses of MeHg for prolonged periods resulted in gradual constriction of the visual fields, impaired motor co-ordination and possibly sensory disturbances. More recently, monkeys exposed to low levels of MeHg from birth were shown to have impaired spatial visual function compared with control animals. As no overt signs of toxicity were found, the investigators suggested that impairment of acuity may be a more sensitive indicator of exposure than constriction of the visual fields.[80] Neurological damage has also been demonstrated in the mouse, rat, ferret, cat,[81] and dog from chronic ingestion of MeHg compounds. Similar peripheral sensory changes were later followed by central nervous system changes as described above. Other workers have noted, in the brains of animals given large doses of MeHg, a decreased uptake of amino acids before signs of poisoning become apparent.[82,83] Damage to the blood–brain barrier has been observed in rats as early as 12 hours after a dose of MeHg.[84] If similar changes occur in man then significant damage to the central and peripheral nervous system could take place before the appearance of clinical features. Recent work has attempted to identify the ultrastructural effects of inorganic and organic mercury in rats following intracerebral injection.[85] The changes which followed, over a wide range of concentrations of mercuric chloride and MeHg, were identical and resulted in neuronal necrosis characterized by a progressive increase in cytoplasmic volume. It is suggested that the neuronal swelling was the result of fluid entry secondary to the inactivation of enzymes such as membrane ATPase. Others[86-8] have demonstrated identical changes in rat brain following oral dosing with both mercuric chloride and MeHg; therefore, although both types of mercury are neurotoxins, it is suggested that it is the relative ease with which organic mercury enters the nervous system rather than any inherent neurotoxicity due to the presence of the methyl radical that accounts for its severe neurological effects.

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Mutagenicity

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In Japan in the middle and late 1950s at Minamata, and again in 1965 at Niigata, mass poisoning of fishermen and their families occurred following consumption of alkylmercury-contaminated fish and seafood.[89] In each episode, a subtle forewarning of the impending disaster was the strange, erratic behaviour of the local cats who had eaten dead seafood washed ashore or had been fed contaminated seafood. An outbreak of MeHg poisoning in cats was reported in Canada following the consumption of fish from a river that had been severely contaminated with mercury discharged from a chloralkali plant. One cat developed acute neurological effects with an ataxic gait, other abnormal movements, uncontrolled howling, and seizures. The total mercury analyses showed high levels in all tissues with 16.4 mg per kg in the brain.[89] In looking at the differential toxic effects of mercuric chloride and methyl mercuric chloride on a freshwater alga the organic mercury salt was found to be highly toxic.[90] It was suggested that the differing toxic effects were due to the amphophilic nature of MeHg favouring interactions with lipophilic cell structures, especially cell membranes.

Mercury compounds have been shown to have haemolytic effects on human, sheep, and rabbit erythrocytes.[91] *P*-chloromercuribenzoate, ethylmercuric chloride, and thiomersal lysed human and sheep red cells less rapidly than rabbit cells, but this effect was less than with mercuric chloride. It was suggested that the lytic ability was due to the number of free positive charges; the inorganic compound has two free positive charges; *p*-chloromercuribenzoate and ethyl mercuric chloride have one free positive charge. These are more potent than thiomersal, which is thought to release a free positive charge in the presence of tissue sulphydryl groups. It is suggested that haemolysis involves the formation of a chelate or co-ordination complex of the mercury ion with a reactive group on the surface of the red cell membrane causing instability and subsequent lysis.

Recent work on rat platelets[92] has demonstrated that PMA affects both platelet membranes and intraplatelet mechanisms. Methylmercuric chloride induced platelet aggregation as an ADP-independent platelet stimulator. The results suggest that these organic mercury compounds could affect blood clotting mechanisms.

Mutagenicity

Mercury compounds have varying effects on genetic material. All compounds are active as C-mitotic agents although the effect of organic compounds is much greater than that of inorganic. Alkyl and phenyl mercury compounds also cause chromosome breakage and to a lesser extent point mutations.[93,94] The genetic activity of mercury compounds was first demonstrated when ethyl mercury phosphate, a fungicide, caused disturbances of mitosis and polyploidy in plant cells.[95] Since then further experimental work has confirmed C-mitotic effects on tissue cultures of HeLa cells with various organic mercury compounds.[96] Methyl mercury chloride has been shown to cause chromosome stickiness and clumping leading to reduced mitotic divisions.[97] MeHg has induced inactivation of the spindle fibres during meiosis, resulting in chromosomal effects like those induced at mitosis. MeHg has also caused an increase in sex-linked recessives, that is XXY nondysjunction, in *Drosophila*.[94] Ramel, in his experiments with *Drosophila melanogaster*, showed that these effects could be detected as genetic abnormalities in the offspring of these fruit flies. From his study of the effects of MeHg on the repair of radiation-induced chromosome breaks he assumed that the chromosome breakage by MeHg was due to its action directly on the chromosome repair and DNA synthesis.[98] Ramel's work provided evidence that organic mercurials can cause genetic alterations by two different mechanisms, one resulting in chromosome aberrations and another in chromosome loss following spindle inhibition. It has been shown that *in vitro* dimethyl mercury at high concentration can completely inhibit meiotic division in mouse ova, and at lower concentrations it can cause chromosome abnormalities.[99] No immediate or delayed effects could be demonstrated *in vivo*; it was therefore suggested that the mouse ovum is protected from the cellular effects of excess mercury, possibly by the zona pellucida, the vitelline membrane, or even the follicular cells.[99] Fertility studies in mice have shown, however, that MeHg affected spermatogonial and premeiotic cells as well as early spermatids; these effects were attributed to its levels in target cells and to its inhibition of spermatogonial DNA synthesis.[100] It has been shown that MeHg consumed by cats in their diet is distributed to the gonads,[101] and also that dose-related reduction in mean litter size per pregnancy occurs after male rats are treated with methyl mercury chloride.[102]

Teratogenicity

On looking at the placental transfer of mercuric chloride, PMA, and methyl mercury acetate in mice, the latter compound was found to be the most easily transferred whereas the two former compounds were blocked to the same degree and only traces reached the fetus,[75] confirming previous work. PMA introduced either intravaginally or subcutaneously in mice was shown to be teratogenic;[103] the abnormalities were confined to the central nervous system. Similar findings were obtained for ethylmercuric phosphate. In mice MeHg crossed the placenta readily and the mercury concentration in fetal erythrocytes was 30 per cent higher than in maternal red cells.[65] Again, when pregnant rats were exposed to a single dose of MeHg this resulted in a fourfold greater concentration of mercury in the fetal brain than in the maternal brain.[104]

Various doses of mercuric acetate and PMA administered intravenously to pregnant golden hamsters on the eighth day of gestation exhibited a delayed growth rate in fetuses, and resorption rates were significantly higher than in

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controls.[105] Exencephaly, encephalocoele, anophthalmia, micrognathia, cleft lip and palate, rib fusions, and syndactyly were observed in the fetuses of treated females. The maternal effects were weight loss, kidney lesions, diarrhoea, slight tremor, and somnolence.[105] In another investigation, embryolethal effects and club foot and hydrocephaly were noted in the hamster.[106] MeHg has also caused cleft palate in mice;[106,107] embryolethal effects and especially cleft palate were noted with higher doses.[108,109] It has been suggested that impaired protein synthesis delays palatal closure.[110] Cranial, facial, and limb abnormalities were seen less frequently.[107,111] Dose-related dysmorphogenesis and growth retardation has also been demonstrated in rats with methyl mercuric chloride, and similar patterns of abnormalities with major ones in the central nervous system.[112] In these investigations the incidence of malformations was dose-related and depended on the timing of the exposure in relation to organogenesis. Acute placental transfer studies in the monkey have shown that MeHg is transported more rapidly to than from the fetus.[113] When pregnant monkeys were given 12–14 weekly doses of MeHg at 0.5–5.0 mg per kg, at this low dose the mothers remained well but 50 per cent of the fetuses died; one of the survivors, which survived for one day, had syndactyly and low birth weight and the other was born with paralysed hind limbs and died after 4 months. At the higher doses of 2.5 mg and 5.0 mg per kg per week the mothers developed typical signs of mercury poisoning and the fetuses aborted.[113]

Delayed teratogenic effects have also been demonstrated. Mice exposed to a low level of MeHg during primary organogenesis have been shown to exhibit postnatal behavioural deviations,[114,115] and immunological deficits not apparent until later in the lives of the offspring.[116] Premature death was also noted. Mice exposed to MeHg both in utero and neonatally, through treated mothers' milk, showed diminished hepatic metabolism of cortisone due to a 30 per cent loss of liver mass.[117] Disturbances in carbohydrate metabolism have also been reported in rats.[118] Fetal, newborn, and postnatal animals from MeHg-treated mothers were investigated: fetal rats showed decreased concentrations of plasma glucose and liver glycogen concentrations and a lower hepatic glucose-6-phosphatase activity compared with control animals; in newborn rats there was impaired glycogen mobilization accompanied by severe hypoglycaemia; and postnatal rats exhibited higher liver glycogen concentration and decreased body weights compared with controls. Adult male rats exposed prenatally to MeHg demonstrated depression of hepatic cytochrome P-450-dependent mono-oxygenase systems.[119] This effect was not seen in immature male or female rats or in adult female rats. Detailed studies showed that this latent teratogenic effect appeared only when exposure to MeHg occurred during early fetal development.

Carcinogenicity

No information on carcinogenicity was found.

Human toxicology

Mercury in all forms is known to be toxic to humans. Some forms, however, are more toxic than others as it is the chemistry of the mercury-containing molecule that determines its biotransformation in the body. Although poisoning by inorganic mercury has been known since ancient times, the considerably greater toxicity of organic mercury compounds has only been recognized more recently.[12] From the toxicological standpoint organic mercury compounds can be divided into two classes: (1) those that tend to break down readily in the body to yield inorganic mercury, and (2) those in which the integrity of the carbon–mercury bond is maintained. In class 1, the aryl organic mercurials, for example PMA, behave more like the inorganic compounds. In contrast, in class 2, alkyl mercurials, that is, the methyl and ethyl organic compounds, are very toxic. They may be absorbed from the lungs, from the gastrointestinal tract, and through the skin, and repeated exposure even in small amounts leads to irreversible damage to localized areas of the central nervous system.

Gastrointestinal effects

Both aryl and alkyl salts are irritant to mucous membranes and when taken by mouth cause nausea, vomiting, and abdominal pain.[120,121] If inhaled, they produce a sensation of dryness and irritation in the nasopharynx and mouth, which can be followed by blistering. With more intense exposure, severe diarrhoea may occur. A metallic taste is noticed with phenylmercuric compounds, and within 24–36 hours stomatitis develops with unpleasant breath, sore gums, and excessive salivation. The gum margins later become discoloured. Alkyl mercury compounds cause little if any salivation or stomatitis. Dysphagia has occurred rarely, as has melaena.[18]

Metabolic effects

If the vomiting and diarrhoea are severe, profound shock may occur. Fever, nausea, and vomiting may follow intravenous administration of organic mercurial diuretics.[10]

Respiratory effects

Inhalation of alkyl mercury compounds causes irritation of mucous membranes of the nose, mouth, and throat shortly after exposure, which usually disappears when exposure ceases.[120] Vapours of the salts easily penetrate the lung alveoli and about 80 per cent is said to be absorbed.[122] With exposure to alkyl mercury salt aerosols, the absorption rate is dependent on particle size and the rate of deposition of the salt in the respiratory tract.[122] Inhalation usually accounts for some absorption from topical applications to the skin.

Cardiac involvement

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Hepatic effects

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Renal effects

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Dermatological effects

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Cardiac involvement

Cardiac effects are uncommon but in severe cases some changes have been noted, namely, an irregular pulse, sometimes with bradycardia. Electrocardiographic examination showed frequent ventricular ectopic beats, prolongation of Q–T interval, depression of the S–T segment, and T inversion.[18]

Hepatic effects

Of 10 subjects exposed to phenyl mercury salts, 4 showed evidence of liver damage, in that they had clinically enlarged livers and mild jaundice, but it is not certain whether they had also been exposed to other substances.[123]

Renal effects

Although organic mercurials are considered to be less toxic to the kidney than inorganic compounds, they have also been shown to produce albuminuria, as reported following exposure to PMA sprayed on skin,[124] and also with ethyl mercury poisoning.[18] Methoxyethyl mercury compounds have caused renal damage together with other systemic effects.[125,126] The nephrotic syndrome has been reported in a patient following exposure to an organic mercury seed dressing[125] and during Mersalyl therapy.[127,128] Initially, evidence indicated that the proximal tubule alone was affected but later reports also demonstrated glomerular damage,[127-9] with thickening of the capillary basement membrane. Similar changes were reported following the ingestion of inorganic mercury-containing preparations or following their topical use for psoriasis. It was suggested that these changes represented an abnormal immune response to the mercurial compound rather than a direct toxic effect on the tubule.[127] Kazantzis[74] stated that it was very likely that a glomerular lesion was involved in all these cases of nephrotic syndrome and it was reasonable to attribute this to an abnormal immune response, relating to a mercury–protein complex. Untoward immediate fatal and non-fatal reactions to intravenous administration of organic mercurial diuretics are considered to be a result of an allergic response. Because of rare instances of fatal ventricular fibrillation, the intravenous route was discontinued.[130]

Dermatological effects

Aryl and alkyl salts are also irritants to skin. Aryl compounds, for example PMA, are much less volatile but have strong corrosive action and will therefore cause blistering of the skin. In a series of 42 cases of toxic effects in lumbermen who were spraying a fungicide containing ethyl mercury phosphate onto newly cut wood, there was no immediate reaction on contact, but after several hours redness and swelling developed, the skin felt hot, and blisters appeared.[131] The lesions, which were slow to heal, appeared similar to burns. Similar lesions of the hands have been mentioned in workers who handled phenylmercuric salts.[124] Fungicidal ointments or solutions containing methylmercury thioacetamide caused four cases (two fatal) of poisoning in Japan.[132] The topical application of another organic mercurial, mercurochrome, has resulted in severe adverse effects in young infants and adults. In 13 infants,[133] the topical application of 2% mercurochrome for the conservative treatment of omphalocele caused pink urine, reddening of the skin, sclerema, progressive oliguria, and central nervous system disturbance. In another case, mercurochrome applied to an infected omphalocele resulted in extensive vesicular lesions and death in an 11-day-old infant.[134] A 2% solution had been applied for 4 days but when fever and bullous lesions appeared 0.5% solution was used instead. Serum mercury levels were found to be 84 μg per 100 ml. Further neonatal deaths have been reported in similar circumstances.[135] In a recent case, four applications of 10% mercurochrome to an omphalocele resulted in death of a newborn baby, reported to be caused by bradycardia secondary to renal failure.[136] Serum mercury levels were raised to 260 μg per 100 ml, and electron microscopy of the proximal convoluted tubule showed mitochondrial microcrystalline aggregates identical to those seen in animal models of mercury-induced renal failure.

Lethal mercury poisoning following the application of mercurochrome to second-degree burns covering over 30 per cent of the body surface area has also been described.[137] Urinary mercury levels were raised 100 times above normal levels. Clinical signs of stomatitis, gastroenteritis, and haemorrhagic enterocolitis were noted. Polyuria followed by anuria occurred, as well as severe central nervous system disturbance. A recent report of toxicity following the use of mercurochrome for the treatment of petrol burns in a 6-year-old child[138] lends weight to the need to consider the efficacy of such products in relation to their serious adverse effects. Intravenous administration of organic mercurial diuretics[10] may be followed by flushing, pruritus, urticaria, and exfoliative dermatitis, together with other general effects.

Penetration of mercury from ophthalmic preservatives

In a study in which single corneas from nine patients were exposed to thiomersal, the concentrations of mercury in the aqueous were found to be similar to those reported to produce systemic effects by organic mercury.[139] PMN used at a concentration of 0.004% may lead to mercurialentis, which is a brownish granular discolouration of the anterior surface of the lens.[140] Thiomersal is more soluble and stable and is unlikely to lead to deposition of the reduced metal. Topical application of thiomersal to rabbits had no toxic effects observable by electron microscopy; but continuous perfusion *in vivo* with 0.0004% thiomersal increased corneal permeability with loss of surface cells, and at 0.01% endothelial perfusion caused irreversible damage with corneal

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swelling. Soft lenses soaked in 0.01% thiomersal produced irritation and conjunctivitis in rabbits after 7 days. It did not influence tear-film wetting of the cornea or contact lenses, or the stability of the tear film itself. An instilled eye-drop disappears within 30 seconds, and as most ophthalmic preparations are instilled four times daily the ocular contact time is about 2 minutes. With soft-contact-lens wearers, however, exposure can occur for several hours daily and therefore the risk of developing adverse reactions is increased. PMA and thiomersal have been shown to be cytotoxic in human conjunctival epithelial cell culture.[141] Although thiomersal has been known to cause both a blepharoconjunctivitis and a punctate keratitis in contact lens wearers,[142] this appears to be an uncommon reaction.

Absorption of mercury from the vagina

The use of PMA, PMN, and other compounds containing mercury as active ingredients in vaginal contraceptives has resulted in significant absorption of mercury, as demonstrated by raised blood levels in women using vaginal suppositories containing PMA 0.4 mg over a 3-month period during which two to six suppositories were used per week.[143] Hypersensitivity to mercury in dental amalgam fillings has been reported following previous exposure to a phenylmercuric salt in a contraceptive jelly.[144]

Absorption of mercury by injection of gammaglobulin

Thiomersal 0.01% is also used as a bacteriostatic agent in commercially available gammaglobulin. The mercury content of the preparation is 50.3 μg per ml. Of 26 patients with hypogammaglobulinaemia who had received regular long-term replacement therapy with pooled human immunoglobulin G, and where the total mercury dosage received was in the range of 4–743 mg, 19 had elevated mercury levels although there was no clinical evidence of mercury toxicity.[145] No correlation was found between urine mercury level and age of the patient, dose of IgG, or duration of the treatment. In another report,[146] a 20-year-old male with congenital agammaglobulinaemia developed signs of acrodynia with pink, scaling, itching palms and soles, flushed cheeks, photophobia, irritability, a fine tremor, and paraesthesia of his fingertips, the only case known to have been caused by ethyl mercury exposure. The urine and blood levels of mercury were raised, 90 per cent of the mercury in the urine but only 50 per cent of that in the blood being in the inorganic form, making it impossible to know which form produced the symptoms.[147] In another case, thiomersal poisoning was reported in a 13-year-old boy who had received 280 mg of mercury over a 3-month period from intravenous plasma supplements to treat protein-losing enteropathy, yet four other patients who had received between 3 and 210 mg mercury developed no acute symptoms or signs in spite of excreting 50–600 μg mercury daily.

Marrow suppression

Aplastic anaemia is alleged to have resulted from the application of 20% mercurochrome to two surgical openings and decubitus areas postoperatively in an adult patient whose greatly raised blood and urine levels before death indicated absorption of mercury as the cause.[148] Neutropenia was noted among other abnormalities in 9 of 10 subjects exposed to phenyl mercury salts; the white cell count returned to normal levels following a period free from exposure.[130] Mercurial diuretics have been described as causing thrombocytopenia and agranulocytosis, but no bone-marrow appearances were included.[10,149]

Central nervous system effects

In poisoning by methyl and ethyl organic mercury compounds, symptoms due to organic disease of the central nervous system are more pronounced than those due to psychotic disturbance.[9] The initial symptoms may be vague complaints of tiredness followed by paraesthesiae which often first affect the face, particularly around the mouth, followed by similar symptoms in the extremities. Later deep sensory disturbances, tremors, ataxia, dysarthria, and hearing impairment may develop. The visual fields may become constricted and in severe cases tunnel vision may be present. Memory and intelligence remain unimpaired even in severe cases where total physical disability has developed. Where exposure has been more severe, symptoms have been acute and the diagnosis has been arrived at more rapidly; such cases have recovered[49] or improved over many months or years. In severe cases, where mercury levels are more than 2 μg per ml whole blood, coma and death may result.

The pathogenesis of the movement disorder is not well understood. Degenerative changes affecting mainly the visual cortex and the granular cell layer of the cerebellum have been found in organic mercury poisoning.[150] Similar changes were reported in adults and infants from Minamata Bay, with occasional involvement of the area striata.[151] Neural degeneration with glial proliferation was found throughout the cerebral and cerebellar cortex of congenital cases.[151,152]

The abnormal movements are like those seen with lesions of the basal ganglia and cerebellum. The ataxia may partly be due to a sensory neuropathy.[153,154] This was confirmed in a further pathological study of chronic Minamata cases: where cerebellar lesions were milder, the nodulus, ovula, and lingula of the vermis and medial surface of the semilunar lobules were most damaged as well as the spinal sensory nerves.[155]

Fetal poisoning

In the 1953–71 Minamata epidemic, 25 infants were born with brain damage.[60] They developed cerebral palsy, chorea, ataxia, tremors, seizures, and mental retardation. The mothers
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retardation. The mothers were heavy fish-eaters but did not demonstrate the typical symptoms apart from mild paraesthesiae. The fact that the infants had not eaten contaminated fish suggests that they had become exposed *in utero*, although it was possible that postnatal exposure could have occurred through breast milk.[152,155] In many cases, MeHg levels in the umbilical cord blood of infants were more than 1.0 ppm,[156,157] and mercury values in the hair of patients and offspring were raised.[158] In Iraq, blood mercury levels of infants born before the epidemic were less than maternal levels and, therefore, probably represented exposure via breast milk only. In infants born during or after the epidemic, blood mercury levels were higher than maternal values; the mercury was therefore acquired *in utero*, during breast feeding, or from both sources. Poisoning *in utero* was suspected in infants less than 2 months old as several had mercury levels above 25 μg per ml blood and demonstrated severe brain damage.[49,159]

In the USSR, in 10 cases of poisoning of pregnant mothers from eating grain treated with ethyl mercury, severe mental retardation occurred in three of their infants, with decreased birth weight and muscle tone in the others.[160] Other cases have been reported[161–3] in which mothers had been exposed through several sources including contaminated fish, meat from domestic animals fed contaminated grain, and direct human ingestion of mercury-treated grain. Two of their infants had neurological abnormalities and severe visual defects.[161,162] As the studies undertaken during the MeHg poisonings in Iraq showed poor correlation between the degree of maternal exposure and mercury concentration of amniotic fluid, it is unlikely that amniocentesis would be helpful in diagnosing fetal involvement.[49]

Mutagenicity

HeLa cells treated with phenyl and alkyl mercuric compounds showed increased abnormal mitosis.[96] Exposure of HeLa S3 cells to increasing concentrations of MeHg for different periods of time resulted in a rapid decrease of DNA, RNA, and protein synthesis followed by cell death.[164] MeHg has been shown to cause an increase in chromosomal aberrations in human lymphocytes following *in vitro* and *in vivo* exposure.[165] Lymphocytes from the cultured blood of 23 people exposed to MeHg in a diet of contaminated fish were compared with those of 16 unexposed controls.[166] There was a significant statistical relationship between the frequency of cells with chromatid aberrations, unstable chromosome-type aberrations, and aneuploidy and blood mercury levels of the exposed subjects.[167] A significant correlation was found between the blood and urine mercury levels and the total number of cells with chromosomal aberrations and frequencies of cells with other non-chromatid type aberrations.[168] Dissociation of the acrocentric chromosomes occurred in metaphases from PMA-exposed subjects,[169] and it has been confirmed that mercury compounds influence some factors regulating the nucleolus-organizing activity.[170]

Teratogenicity

In Minamata, human fetal lesions were reported to be different from those in adults because there was more diffuse cerebral cortical involvement and fetal brain hypoplasia and malformations occurred frequently.[152] Cleft palate does not appear to have been reported.

Carcinogenicity

No data on human carcinogenicity were found.

Adverse reactions to organic mercury used therapeutically

Twenty-seven adverse effects directly attributable to organic mercury preparations have been reported to the UK Committee on Safety of Medicines between 1964 and February 1986. In 10 cases Mersalyl was implicated, causing gingivitis in one case and a rash in two others. Sensitivity reactions caused vomiting and diarrhoea in one patient, and cyanosis and malaise in another. Peripheral neuropathy and paraesthesia was reported in one case. Of the three fatal cases, cardiac arrest occurred in one and acute renal failure in two cases. Hydrargaphen, an organic mercury compound used in topical preparations for the skin and vagina, was reported to have caused 15 adverse effects. These were rash and urticaria (4), hirsutism (2), and one each of contact dermatitis, acrodynia, genital pruritus, vaginitis, virilism, generalized oedema, and weight loss. Two infants were born with congenital abnormalities, but these reports could not be assessed, as details of the timing and duration of use of the vaginal preparation during the pregnancies were not provided. Thiomersal, which is present as a preservative in many ophthalmic preparations, was reported to have caused a local reaction in two cases. It is possible, however, that more reactions to organic mercury preservatives in ophthalmic products will come to light following the introduction of reporting of adverse reactions by ophthalmic opticians since the end of 1985.

Poisoning due to occupational exposure in the UK

Over the past 25 years, six cases of occupational exposure have been reported to the Health and Safety Executive. Two were fatal: these occurred in the early 1960s, and were due to ethyl mercury chloride. In the case where some details were available death was due to encephalopathy and the 24-hour urine specimen contained 2600 µg mercury. The last cases were reported in 1971, they were both mild and recovered.

Treatment

Treatment consists in removing the cause, general supportive measures, the use of chelating agents, and the provision of appropriate rehabilitation

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measures like speech- and physiotherapy. In chronic poisoning, although the excretion of mercury is increased with chelating agents the clinical condition has not invariably improved, which suggests irreversible damage before therapy was commenced.[55,161] It has been shown that BAL increased the urinary excretion of mercury in mice given an injection of PMA, and there was also an increase of mercury in the brain of treated mice compared with those which had been given only the organic mercury compound.[171] This finding questioned the use of BAL in organic mercury poisoning. Treatment of PMA poisoning with BAL chelation and supportive therapy was successful, however, in a very young child who had swallowed an unknown amount of a 10% solution.[172] She developed epiglottitis, oesophagitis, pharyngitis, pneumonia, mild renal failure, and dermatitis. The peak blood mercury level was 104 μg per ml. Follow-up at 2 months showed no sequelae. Other patients have been similarly treated with complete recovery.[12,173] Calcium disodium edetate is of limited value due to the relatively slight degree of dissociation of MeHg to inorganic mercury ions. In rats, penicillamine (PEN) reduced fetal brain MeHg concentrations and prevented morphological changes in the brain.[105] During the outbreak of organic mercury poisoning in Iraq, *N*-acetyl-d,l-penicillamine (NAP) was tried, with mixed success.[49,174] It appeared to increase MeHg excretion in some individuals but in others little effect was seen. There do not appear to be any reports demonstrating efficacy of PEN in reducing human fetal damage due to MeHg poisoning. As only a small proportion of total blood MeHg is contained in the plasma, conventional haemodialysis is of little value. It has been shown that *l*-cysteine infused into the arterial blood entering the dialyser can convert MeHg into a diffusible form.[175] Both free cysteine and the methyl mercury–cysteine complex formed in the blood diffuse across the membrane into the dialysate.

Renal toxicity has been known to occur after prolonged administration with high doses or following a single excessive dose of a mercurial diuretic.[176] If renal failure supervenes, peritoneal dialysis or haemodialysis has to be considered but as both these forms of treatment have not proved effective in all cases, in spite of prior treatment with dimercaprol, the use of a dialysis membrane of low solute resistance could allow more efficient removal of the dimercaprol–mercury chelate.[177] Pyridoxine-5-thiol has been shown to reduce MeHg concentrations in the brain and liver of rats.[178] Polythiol resin given as a 10% concentration with food doubled the rate of MeHg excretion in mice.[179] Normally about 10 per cent of ingested MeHg is excreted into bile[69] with only 3 per cent being excreted in the faeces, indicating that a large amount is reabsorbed. The polythiol resin combines with MeHg in the intestinal tract and thereby interrupts the enterohepatic circulation and prevents reabsorption.[179] By increasing faecal excretion of MeHg the blood level is lowered and therefore encourages its movement from the tissues to the blood. Clinical studies have shown that thiol resins effectively increase MeHg excretion,[47,179] and further studies have demonstrated that the dose of acetyl-

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penicillamine can be reduced by combined treatment with them.[180] Sodium 2,3-dimercaptopropane-1-sulphonate (DMPS) has been shown to increase the urinary excretion of MeHg in rats.[181,182] Clarkson and colleagues[183] have confirmed the value of PEN, NAP, DMPS, and polythiol resin clinically; all four treatments significantly reduced the half-life of MeHg in blood: DMPS to 10 days; polythiol resin to 20 days; NAP to 24 days; and PEN to 26 days. They suggest that treatment with these mercury-binding agents is justified even some weeks or moths after exposure. As polythiol resin is not absorbed it could be useful in the treatment of pregnant women exposed to organic mercury.

In the Iraq epidemic, autopsy material from humans and experimental animals showed deposition of mercury and cellular damage mainly in the cerebellum and the cortex of the occipital and parietal lobes. Later, experimental studies showed marked damage to the peripheral sensory nervous system. Clinical electrophysiological tests, however, showed no abnormalities in conduction velocities, thresholds, or latencies.[184,185] Neostigmine administration produced marked improvement in affected patients for the alleviation of symptoms of weakness and fatigue. It appeared to be a useful drug in selected patients suffering from MeHg poisoning.[185] Whether it speeds up permanent recovery has yet to be demonstrated.

The interaction between compounds of selenium and those of mercury have been studied fairly extensively since the 1950s. Inorganic selenium, especially selenite, has been shown to inhibit neurotoxicity due to MeHg given simultaneously in the diet to mice,[110] Japanese quail,[186] and rats.[187] Such an effect is also exerted, although to a lesser extent, by selenium naturally present in fish. Selenite did not increase the rate of breakdown of MeHg given to rats; it increased mercury concentration in the liver, spleen, and in the brain, and a decrease in the blood content was observed.[188] It has been suggested that the differential susceptibility of different areas of the brain to MeHg damage might be related to regional differences in selenium concentration. This has been confirmed in monkeys where minimal neuropathological changes were observed in areas with high selenium concentrations in the brain but marked damage in areas with low selenium concentrations. Parizek[189] has discussed the interactions between selenium and mercury and suggested that selenium decreases mercury toxicity by competitive binding to sulphydryl groups or by forming selenium–mercury complexes. More recently sodium selenite has been reported to prevent the induction of sister chromatid exchange by MeHg;[190] the mechanism is stated to be by mutual antagonism in their ability to cause DNA damage by the formation of bis-methylmercuric selenide. The addition of selenite to the diet of laboratory animals has also been shown to reduce the toxicity of mercury in relation to growth rates and survival rate,[188] as well as fetal anomaly rates.[109] Other investigators, however, have not been able to confirm these findings.[191] It appears therefore that selenium does not uniformly prevent MeHg toxicity: its effect appears to
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Epidemiology

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Epidemiology

The first reported epidemic due to organic mercury occurred in Japan in the 1950s. Methyl chloride, used as a catalyst in the manufacture of vinyl chloride, was discharged in the effluent from a chemical plant into Minamata Bay, Japan. This inorganic form of mercury was converted to MeHg by bacteria under the anaerobic conditions[192,193] in the silt at the bottom of Minamata Bay. The MeHg was concentrated in marine food chains and, as a result, in the fish.[194] Local fishermen and their families who consumed fish as a large portion of their diet were poisoned by the contaminated fish. The offspring of pregnant women were born with brain damage and developed abnormalities of the central nervous system as previously mentioned, but the mothers who were heavy fish-eaters had no clinical symptoms apart from mild paraesthesiae, and as their infants had not eaten fish it suggested that the neurological damage from toxicity was acquired *in utero* or postnatally from breast milk.[152] Those villagers who were severely affected developed neurological symptoms including mental confusion, convulsions, and coma. About 40 per cent of affected individuals died. Cats, crows, waterfowl, and fish were affected as well.[67] Experiments showed that the condition could be produced by feeding fish and shellfish from the bay to mice, rats, and cats. These fish and shellfish contained 9–24 μg MeHg per g. From 1959–1971, a total of 134 cases were reported, including 78 adults and 56 children; during this period 25 infants were born with brain damage. From 1955 to 1959 about 6 per cent of the children born in the area developed cerebral palsy.[67] Further investigations up to the mid-1970s have revealed over 800 cases of poisoning and over 3000 suspected cases.[195] In 1964, a similar epidemic occurred in Niigata, Japan, again due to consumption of contaminated fish. About 46 cases were reported initially, but by the late 1970s about 650 cases had been identified.[195]

One of the first outbreaks associated with mercurial fungicides was in Pakistan, in 1961, when over 100 people developed chronic mercurial poisoning after eating seed that had been distributed for planting.[19] The worst outbreaks, however, were in Iraq with ethyl mercury *p*-toluene sulphonanilide used as a pesticide in barley and wheat seed dressing.[18,193,194] Farmers supplied with the seed were warned against consuming it, but some farmers thought that washing the seed with water would rid it of the mercury and they then used it for making domestic bread. A total of 100 sporadic cases, with 14 deaths, occurred in northern Iraq in 1956, and a further larger epidemic was seen in central Iraq in 1960, with an estimated 1000 people affected.[19] In

Guatemala, during the wheat-growing seasons of 1963 to 1965, 45 people were affected and 20 died due to methyl mercury dicyandiamide-treated seed. In 1969, in New Mexico, three of five members of a family were poisoned following consumption of meat of hogs which had been fed seed grain that had been treated with a similar fungicide.[196]

In 1971–2 over 6500 cases of organic mercury poisoning occurred among farmers and their families in Iraq.[49,197,198] Then, again, they had made bread at home from grain treated with a MeHg fungicide. The onset of symptoms was gradual, with a latent period between 16 and 38 days after last eating contaminated bread. The severity of the signs and symptoms was dose-dependent[199] and included muscle weakness, paraesthesiae, ataxia, dysarthria, hyperreflexia, intention tremor, and muscle pain.[198] Although the clinical picture in some patients resembled peripheral neuropathy,[184] tests of motor and sensory function failed to confirm this.[185] It was suggested that degenerative changes that had been demonstrated in the postcentral cortex were responsible for the sensory symptoms. Visual disturbances also occurred in half the cases; other symptoms included headache, sleep disturbances, dizziness, and irritability. All age groups were affected, the largest group being children aged 1–9 years. There were over 450 deaths.[198] Infants showed varying degrees of nervous system damage similar to congenital Minamata disease, namely, cerebral palsy, blindness, deafness, and mental retardation. Patients who were mildly affected recovered completely, those who were moderately disabled improved gradually over months, but those most severely poisoned died early or became severely handicapped, recovering only partially over a period of many years.[49,200] In the Minamata outbreaks the poisoning from contaminated fish was not recognized for several years, by which time the total body burden of mercury was very high. Because the Japanese reports[197] stated that most patients were permanently affected and that their condition was progressive, many workers in this field assumed that the condition was irreversible. The epidemic in Iraq, however, was more acute and the diagnosis was more rapid and once the intake stopped the concentration of mercury fell 2–3 months after exposure had ceased.[49]

Many reports have been published[49,159,201–4] on the investigations carried out on the Iraqi mothers and their children to attempt to clarify the influence of MeHg exposure *in utero* and postnatally. These studies showed that the mothers with the most severe clinical signs of poisoning had, on average, higher blood mercury concentrations than the groups with milder symptoms or those who were asymptomatic.[201] They confirm the free placental transfer of MeHg and that the degree of psychomotor damage of exposed infants was dose-dependent, and could be correlated with peak maternal hair mercury levels.[202] A recent investigation[203] on 84 Iraqi mothers and their infants exposed to MeHg during pregnancy has again demonstrated that symptoms and signs in the infants could be roughly related to maternal mercury hair levels. Severe neurological signs were seen in 5 children whose peak maternal hair mercury levels were

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as of 1963 to 1965, 45 people
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and 38 days after last eating
ns and symptoms was dose-
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muscle pain.[198] Although the
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this.[185] It was suggested that
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hair mercury levels were 165–320 ppm; minimal symptoms in mothers and children with peak maternal hair levels below 68 ppm; and minimal neurological signs in children when peak maternal hair mercury levels were between 68 and 180 ppm. Children exposed to MeHg during the second trimester were the most severely affected. This is compatible with neuropathological findings[205] of impaired neuronal migration in brains that had been exposed in the third and fourth months of pregnancy, which is a critical period for neuronal migration.

Studies have also shown that MeHg excreted in breast milk is related to maternal blood mercury levels and that the infants' blood mercury levels were maintained by additional amounts transmitted in their mother's milk.[201,204] Follow-up revealed that those infants exposed postnatally through being breast-fed had less serious central nervous system effects than those exposed prenatally. Continued follow-up has also revealed a raised childhood mortality, which appeared to be due to intercurrent infection in children who had cerebral palsy. The mothers of these children had maximum hair concentrations in the first trimester that exceeded those of mothers whose infants were also exposed in the first trimester as well as the other two trimesters.[204]

Organic mercury compounds have long been recognized as effective fungicides and have been widely used for this purpose, in agriculture and in the paint and paper industries. PMA has been employed in the prevention of slime formation in the manufacture of paper. It is also used, normally in powder form, as a seed dressing to prevent various seed-borne diseases of cereals, and for this purpose it is often combined with a small amount of an alkyl salt, such as ethyl mercury chloride.[206] The manufacture of phenyl and tolyl mercury acetates in large quantities in the UK and Germany had been undertaken by automatic methods in enclosed apparatus.[1] The products are used mainly in the form of dusts but sometimes in solution. Apart from an occasional burn on the skin in handling these chemicals no serious accidents have been reported.[1] Because of technical advantages there has been a tendency to replace PMA as a seed dressing by methyl mercury dicyandiamide, which is applied to the seed as a liquid. Although this action may have been taken for its practical advantages, the risk of exposure to the much more toxic alkyl salts is increased and the change is, therefore, not desirable.

The danger of exposure to alkyl mercury has been recognized since 1865 when two laboratory technicans died from dimethyl mercury poisoning.[2,3] Further sporadic episodes were reported in the 1940s,[1,12,120,150] and from the 1950s large-scale exposure has occurred following the consumption of poisoned fish or bread, as described earlier, in the Japanese and Iraqi epidemics. Raised concentrations in fish have resulted from contamination of inland and coastal waters by pollution from natural and industrial sources.[67] Micro-organisms in river and lake sediments convert various inorganic and organic mercury compounds into the most toxic compound, MeHg. Fish take up MeHg directly through their gills and indirectly by eating contaminated food.

Because MeHg has an excretion half-time in fish of up to several hundred days it accumulates in concentrations thousands of times greater than in the surrounding water. As a result it has also given rise to high concentrations in birds and animals that feed on them,[132] for example, sea eagles. The use of alkyl mercurial salts, mainly MeHg, in Sweden from the mid-1940s until 1966 led to an accumulation of mercury in seed-eating birds, such as pheasants and wood pigeons, and in small rodents. A number of other terrestrial birds of prey have shown raised mercury levels, as have been similarly reported in seed-eating birds; in the Netherlands, cases of poisoning occurred. Reduced hatchability and a high frequency of dead and malformed chicks was reported for eggs with high mercury levels from symptom-free hens.[132] Mercury is strongly bound to fish protein and the complex has not been found to be broken down by cooking.[193] Poisoning occurred in Minimata and Niigata in Japan after consumption of boiled, fried, or raw fish. Other than fish, most foods do not contain mercury in sufficient concentrations to be a health danger, although MeHg-treated seed in Sweden resulted in contamination of many foods, for example eggs, pork chops,[207] pig's liver, and reindeer liver and kidney.[132]

Other populations with long-term exposure to MeHg in fish have been studied,[208-10] and although hair and blood MeHg levels were raised in many individuals there was no convincing clinical evidence of toxicity. In the UK, studies performed in fishing communities and groups with an increased fish consumption have failed to reveal mercury levels associated with adverse effects.[211,212] Further clarification is therefore needed on the question of clinical toxicity, or its absence, in relation to the period of exposure in varying circumstances in different communities.

Discussion

Although there are no statutory requirements for medical examination of workers in industries involving the use of mercury, quantitative examination of mercury in the urine may be helpful in indicating over-exposure. One needs to bear in mind that individual variations in mercury output are considerable, and a change in excretion pattern of an individual may be more significant. For alkyl mercury compounds an amount above 30–60 μ per l is considered to be significant as long as the specific gravity is about 1016.[9] Red cell analysis provides a better indicator of absorption of alkyl mercury salts; the maximum permissible level should be 0.1 μg per ml (10 μg per 100 ml) whole blood. Doubt has been cast on the value of urine analysis as a measure of exposure and, although routine medical inspections are desirable, in the case of alkyl salts the first signs of poisoning may be due to neurological damage. Therefore, if cases of poisoning are to be prevented, the manufacture of methyl and ethyl mercury compounds should be strictly

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controlled. As phenyl and tolyl mercury compounds are effective fungicides that are less dangerous and can be handled with safety, only these should be manufactured.[1] In the factory, adequate precautions must be taken. Wherever there is a dust or vapour hazard, the atmospheric concentration of mercury should be maintained below the toxic limit by the provision of suitable ventilation. Following a spillage or during maintenance and cleaning operations, full protective clothing, including a respirator, should be used. Adequate precautions must be taken to avoid skin contamination and, if it occurs, immediate steps must be taken to flood the affected area with running water. Eating and smoking must not be permitted on sites where organic mercury compounds are handled. The whole manufacture, including final packing of the dust, should be carried out mechanically if possible. Regular atmospheric determinations of mercury are also desirable. The maximum permitted limit in the atmosphere for alkyl mercury salts is 0.01 mg per cubic metre and for aryl salts 0.1 mg per cubic metre.[199]

The use of alkyl mercury seed dressing was prohibited in Sweden in 1967 and this led to a substantial decrease in the levels of mercury in seed-eating birds and their predators[213] as well as in the terrestrial food chains and in animal foodstuffs.[131] The use of preservatives in the paper and pulp industries was banned in Sweden and Finland in 1968 and has been declining in other countries also. Effluent from chloralkali plants was the main source of mercury pollution of US waters until the 1970s when controls were imposed, following which discharges fell sharply. A similar decrease in mercury discharge was reported from Canada, Sweden, and other countries.[214] In the UK, use of mercury in certain applications was deliberately reduced. In the paper and pulp industry, mercurial slimicides were abandoned in the early 1970s and mercurial fungicides are seldom used in adhesives.

In 1975, a Joint Food and Agriculture Organization/World Health Organization (FAO/WHO) meeting on the use of mercury and alternative compounds as seed dressings made two recommendations.[215] Firstly, that the use of mercurial fungicides should never be permitted for treating seeds to be exported for production of food and secondly, that dressed cereal grains should be immediately and permanently distinguishable from undressed seed by the addition of a permanent colour or taste. Finally, doctors everywhere needed to be made aware of symptoms of mercurial poisoning and to be alert to the possibility of an epidemic whenever there were outbreaks of an unexplained illness, especially in rural areas.[215] In the UK, agricultural purposes, which accounted for about 5 per cent of mercury usage, declined and the less toxic phenyl mercurial compounds were used wherever possible; more recently even these have been replaced by non-mercurial seed treatments, while others are being evaluated in other European countries.

According to the report from the Department of Environment[216] most UK population exposure to mercury is well below internationally accepted safety levels. Dietary intake averaged 0.035–0.070 mg per week, of which 0.014-

0.035 mg was in the form of MeHg compounds. These levels are well below the tolerable limits of 0.30 mg per week, including not more than 0.20 mg MeHg, proposed by the Joint FAO/WHO Expert Committee in 1972. Marine fish can contain up to 0.3 ppm and freshwater fish about 0.5 ppm: it is therefore important to monitor levels regularly. The Control of Pollution Act 1974 empowers regional water authorities to control the discharge of toxic materials, including mercury, into rivers and coastal waters according to EEC Directives 82/176/EEC and 84/156/EEC. The maximum limit for water intended for consumption is 1 μg per l (0.001 ppm). An EEC directive on cosmetics excludes mercury and its inorganic and organic compounds from use in such products, with exemption for two compounds of mercury used as preservatives at low concentrations in eye products.

The fetal central nervous system seems to be more vulnerable to the effects of MeHg than that of the mother or of older children. In general, when the intake of MeHg has ceased, mothers and older children showed gradual improvement and even complete recovery, whereas prenatally exposed infants usually showed evidence of permanent damage. This is because the developing fetal and infant brain is more susceptible to the toxic effects of MeHg. A 5-year follow-up has also revealed a high childhood mortality.[203] It is suggested that neuropathological[205] and biochemical changes[112-19] may be the mechanisms partly responsible for the behavioural deviations and mental deficiency in the animal species investigated. It is not clearly understood as yet how much such biochemical 'damage' limits normal growth and development of the central nervous system, although decreased protein synthesis and DNA levels, alteration in carbohydrate metabolism, and disturbed lipid metabolism probably all contribute to overall neurotoxicity.[195] In view of the potential danger to the fetus it has been recommended that pregnant women should not work in areas where raised atmospheric levels of mercury compounds would be expected. Additionally, pregnant women should not be exposed to MeHg compounds and should not eat more than 350 g of fish per week,[67] as there are data indicating that extreme consumers of fish may exceed the FAO/WHO Provisional Tolerable Weekly Intake (PTWI) of 0.2 mg MeHg established for adults. It has been previously stated[75] that 50 to 125 μg per g MeHg in hair is associated with the earliest signs of toxicity in the adult population. Recent research,[202,203] however, suggests that pregnant women and the fetus could have an increased sensitivity to mercury and that uptake by the fetus may be twice that of the mother. Mercury hair levels and the dose-response curves have led to the suggestion that the threshold for effect in pregnancy could be about 30 μg per g in hair (which is about half that proposed by WHO) and 100 ng per ml (10 μg per 100 ml) in blood. For the fetus it is proposed that the threshold should be accepted as 50 ng per ml and 15–20 μg per g for maternal blood and hair mercury concentrations respectively.

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organic mercury compounds *in vivo* have demonstrated genetic damage. It has been shown that MeHg is found in gonads[101] and affects fertility[102] which, it is suggested, could be due to preimplantation loss, and such loss could be due to the induction of dominant lethals. It has also been shown that sensitivity to mercury varies in different animal species. Inherited nondysjunction induced by MeHg has been shown in *Drosophila*,[94] in which it is much easier to detect and to relate the effect to a particular exposure than it would be in a human population.[98] There does not appear to be any information on whether chromosomal aberrations or aneuploidy induced by such compounds are inherited in man.[98]

Most patients with hypogammaglobulinaemia or agammaglobulinaemia are theoretically at risk from exposure to organic mercury and although only few clinical effects have been reported [146,147] doctors responsible for such patients should be aware of the need for continuous supervision to detect any evidence of toxicity that may occur during long-term replacement therapy with immunoglobulin. A similar problem may arise when other plasma supplements are used repeatedly.[148] Multidose vaccines and allergy-testing extracts[217] contain a mercurial preservative, usually 0.01% thiomersal, and may present problems occasionally in practice. It is, therefore, now accepted that multidose injection preparations are undesirable and that preservatives should not be present in unit-dose preparations.

The use of phenylmercuric salts in contraceptive jellies may very rarely induce hypersensitivity to mercury given again in any form, for example, in dental amalgam fillings.[145] This should be kept in mind when patients exposed to mercury develop a diffuse symmetrical erythema mainly in the flexural areas, with miliary pustules, and with or without purpura, or a vesicular rash following exposure, as this suggests a hypersensitivity reaction from previous exposure, perhaps to the use of mercurochrome as an antiseptic.[218] Mercurochrome is still being used as a topical antibacterial agent in some neonatal units, even though it is only weakly bacteriostatic. Moreover, there is published evidence that topical application is associated with potential hazards and even death.[133,136] The use of such a toxic substance when its efficacy is doubtful is difficult to justify, especially when less hazardous and more effective measures are available. Mercurochrome is also included in first-aid kits,[219] in which, as it is only feebly active even as a bacteriostatic agent, it appears to play no useful role. Another topical application containing an organic form of mercury was used in large quantities on an infant with a napkin rash and caused mercury intoxication.[220] As such preparations can be purchased from a pharmacy adequate prevention of such occurrences is difficult and one wonders whether such practices should not be discouraged, especially as there are many less hazardous preparations on the market. The use of MeHg preparations for fungal infections[132] appears to be most unwise. Fortunately, the use of mercurial diuretics has been abandoned in favour of safer oral preparations. The adverse effects of active drugs may be acceptable depending on the therapeutic value, but ill effects arising as a result of preservatives are much less so. Perhaps we should now consider replacing organic mercurial preservatives in medicinal products.

Acknowledgements

I wish to thank Dr J.P. Griffin for his encouragement; Mrs L. Davidson for checking the chemistry section; my medical and scientific colleagues for helpful comments; and Miss J. Raymond for secretarial assistance. Use of CSM adverse reaction data is acknowledged. The views expressed are personal and not necessarily those of the Department of Health and Social Security.

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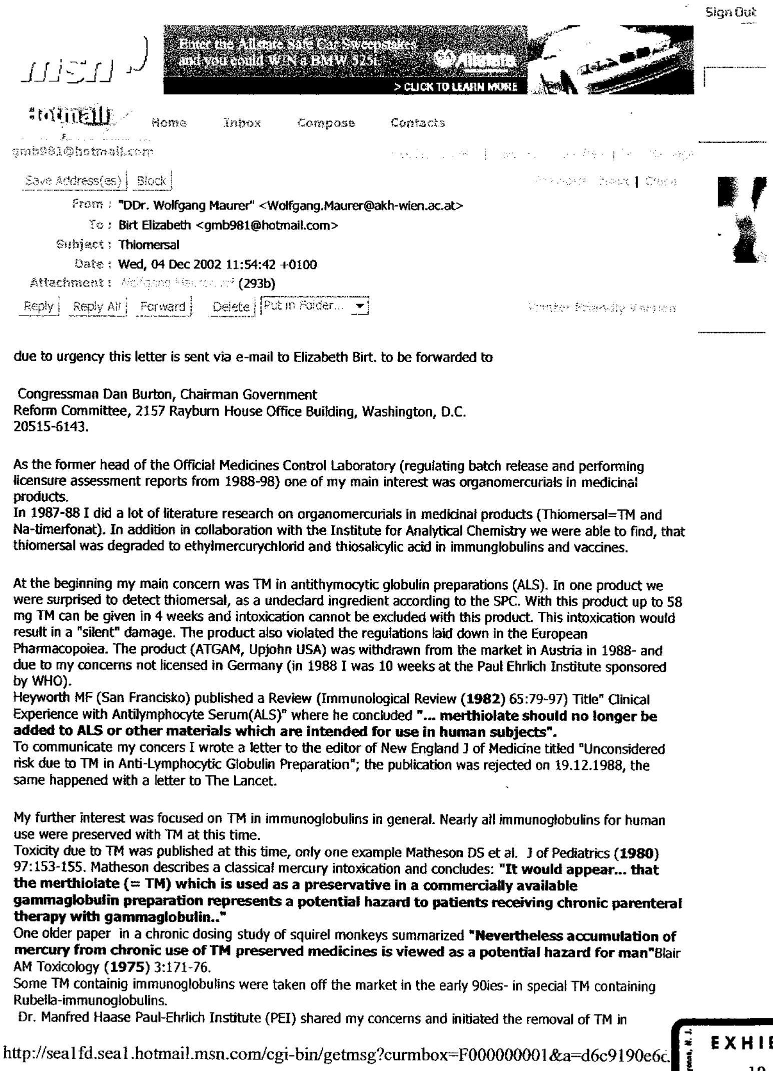

From : "DDr. Wolfgang Maurer" <Wolfgang.Maurer@akh-wien.ac.at>
To : Birt Elizabeth <gmb981@hotmail.com>
Subject : Thiomersal
Date : Wed, 04 Dec 2002 11:54:42 +0100
Attachment : Wolfgang Maurer.vcf (293b)

due to urgency this letter is sent via e-mail to Elizabeth Birt. to be forwarded to

Congressman Dan Burton, Chairman Government
Reform Committee, 2157 Rayburn House Office Building, Washington, D.C.
20515-6143.

As the former head of the Official Medicines Control Laboratory (regulating batch release and performing licensure assessment reports from 1988-98) one of my main interest was organomercurials in medicinal products.
In 1987-88 I did a lot of literature research on organomercurials in medicinal products (Thiomersal=TM and Na-timerfonat). In addition in collaboration with the Institute for Analytical Chemistry we were able to find, that thiomersal was degraded to ethylmercurychlorid and thiosalicylic acid in immunglobulins and vaccines.

At the beginning my main concern was TM in antithymocytic globulin preparations (ALS). In one product we were surprised to detect thiomersal, as a undeclard ingredient according to the SPC. With this product up to 58 mg TM can be given in 4 weeks and intoxication cannot be excluded with this product. This intoxication would result in a "silent" damage. The product also violated the regulations laid down in the European Pharmacopoiea. The product (ATGAM, Upjohn USA) was withdrawn from the market in Austria in 1988- and due to my concerns not licensed in Germany (in 1988 I was 10 weeks at the Paul Ehrlich Institute sponsored by WHO).
Heyworth MF (San Francisko) published a Review (Immunological Review (**1982**) 65:79-97) Title" Clinical Experience with Antilymphocyte Serum(ALS)" where he concluded **"... merthiolate should no longer be added to ALS or other materials which are intended for use in human subjects".**
To communicate my concers I wrote a letter to the editor of New England J of Medicine titled "Unconsidered risk due to TM in Anti-Lymphocytic Globulin Preparation"; the publication was rejected on 19.12.1988, the same happened with a letter to The Lancet.

My further interest was focused on TM in immunoglobulins in general. Nearly all immunoglobulins for human use were preserved with TM at this time.
Toxicity due to TM was published at this time, only one example Matheson DS et al. J of Pediatrics (**1980**) 97:153-155. Matheson describes a classical mercury intoxication and concludes: **"It would appear... that the merthiolate (= TM) which is used as a preservative in a commercially available gammaglobulin preparation represents a potential hazard to patients receiving chronic parenteral therapy with gammaglobulin.."**
One older paper in a chronic dosing study of squirel monkeys summarized **"Nevertheless accumulation of mercury from chronic use of TM preserved medicines is viewed as a potential hazard for man"**Blair AM Toxicology (**1975**) 3:171-76.
Some TM containig immunoglobulins were taken off the market in the early 90ies- in special TM containing Rubella-immunoglobulins.
Dr. Manfred Haase Paul-Ehrlich Institute (PEI) shared my concerns and initiated the removal of TM in

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EXHIBIT
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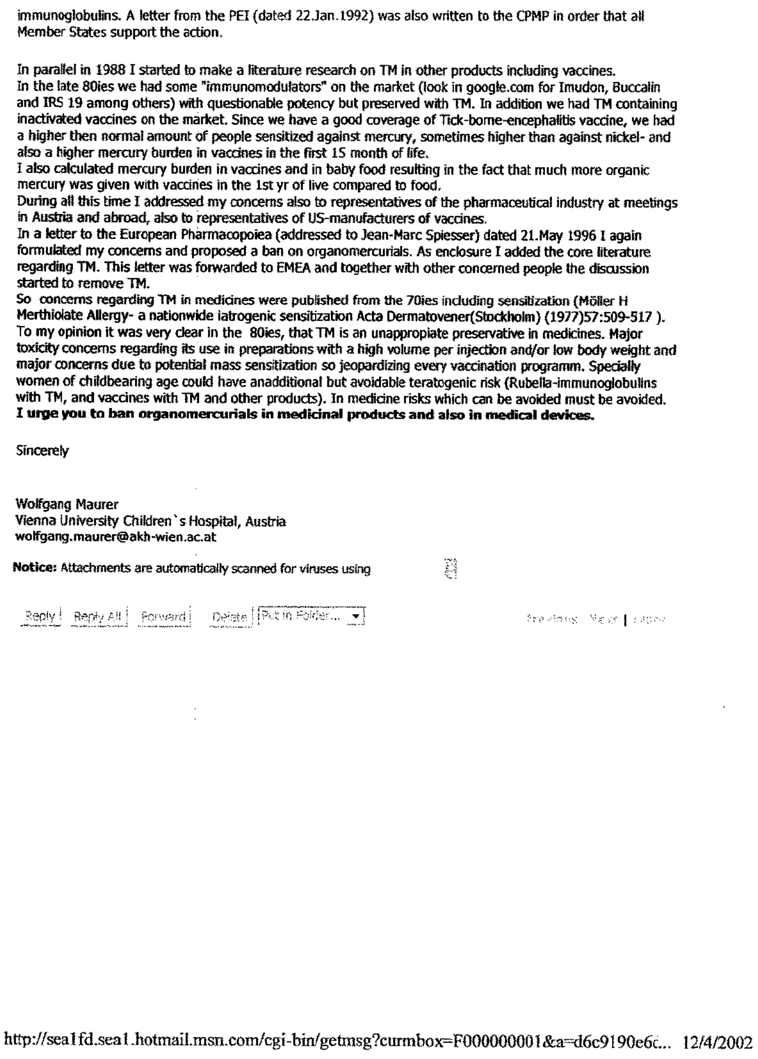

immunoglobulins. A letter from the PEI (dated 22.Jan.1992) was also written to the CPMP in order that all Member States support the action.

In parallel in 1988 I started to make a literature research on TM in other products including vaccines.
In the late 80ies we had some "immunomodulators" on the market (look in google.com for Imudon, Buccalin and IRS 19 among others) with questionable potency but preserved with TM. In addition we had TM containing inactivated vaccines on the market. Since we have a good coverage of Tick-borne-encephalitis vaccine, we had a higher then normal amount of people sensitized against mercury, sometimes higher than against nickel- and also a higher mercury burden in vaccines in the first 15 month of life.
I also calculated mercury burden in vaccines and in baby food resulting in the fact that much more organic mercury was given with vaccines in the 1st yr of live compared to food.
During all this time I addressed my concerns also to representatives of the pharmaceutical industry at meetings in Austria and abroad, also to representatives of US-manufacturers of vaccines.
In a letter to the European Pharmacopoiea (addressed to Jean-Marc Spiesser) dated 21.May 1996 I again formulated my concerns and proposed a ban on organomercurials. As enclosure I added the core literature regarding TM. This letter was forwarded to EMEA and together with other concerned people the discussion started to remove TM.
So concerns regarding TM in medicines were published from the 70ies including sensitization (Möller H Merthiolate Allergy- a nationwide iatrogenic sensitization Acta Dermatovener(Stockholm) (1977)57:509-517).
To my opinion it was very clear in the 80ies, that TM is an unappropiate preservative in medicines. Major toxicity concerns regarding its use in preparations with a high volume per injection and/or low body weight and major concerns due to potential mass sensitization so jeopardizing every vaccination programm. Specially women of childbearing age could have anadditional but avoidable teratogenic risk (Rubella-immunoglobulins with TM, and vaccines with TM and other products). In medicine risks which can be avoided must be avoided.
I urge you to ban organomercurials in medicinal products and also in medical devices.

Sincerely

Wolfgang Maurer
Vienna University Children`s Hospital, Austria
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The European Agency for the Evaluation of Medicinal Products
Human Medicines Evaluation Unit

TELEFAX MESSAGE

DATE:	29 June, 1999	**REF:**	EMEA/19890/99
TO:	Dr Elaine Esber FDA	**FAX:**	001 301 827 0644
FROM:	Fernand Sauer Executive Director	**PHONE:** **FAX:**	+44.171.418.8409 +44.171.418.8440
RE:	Thiomersal	5 PAGES –	

Number of Pages (including cover sheet):

Message:

Dear Dr Esber,

As agreed, please find below a brief update on thiomersal:

As you are aware on 19 April 1999 the EMEA convened a meeting with Interested Parties to discuss the recommendations of the CPMP Working Document (CPMP/2286/98). Dr. Norman Baylor represented the FDA at this meeting. Representatives of the European Pharmacopoeia, WHO, and relevant manufacturers organisations (EFPIA, EVM, EAPPI, EPFA, AESGP and Ophthalmic Manufacturers) also participated.

In follow-up to that meeting, the CPMP's Multidisciplinary Group on Thiomersal convened on 17 May 1999 to review the conclusions and recommendations of the Working Document on Thiomersal and to propose a plan for future action.

A revised Working Document (CPMP/2286/98 Rev 1) outlining the CPMP's final conclusions and recommendations on thiomersal was adopted by the Committee on 23 June 1999. A copy is attached for your information: you may use it freely in today's meeting. Please note that this document has not been released to the public since the following further actions have been requested to CPMP working parties:

- the CPMP's Pharmacovigilance Working Party will propose the wording of a European class warning on sensitisation for the Summary of Product Characteristics (SPC) and Package Leaflet of products containing thiomersal.
- the CPMP's Biotechnology Working Party (BWP) will prepare a concept paper and draft guidance to assist manufacturers in reformulating vaccines to reduce or eliminate organomercurial preservatives. The BWP will continue to work in close collaboration with the EVM.

We would be very interested in hearing about the outcome of the FDA's meeting on thiomersal. In the meantime should you require any further information regarding any of the above please do not hesitate to contact Noël Wathion (tel: +44 171 418 8592 fax: +44 171 418 8668).

Yours sincerely,

Fernand Sauer

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PENGAD-Bayonne, N. J.
EXHIBIT
12

Working Document from the Multidisciplinary Group on Thiomersal

Introduction

Thiomersal is an organomercuric preservative mainly used in vaccines, immunoglobulins and some other medicinal products. Its antimicrobial action is related to the release of ethylmercury, after either spontaneous or enzymatic breakdown of thiomersal into ethylmercury and thiosalicylate.

Background

In January and February 1998, the CPMP Biotechnology Working Party circulated a report on the use of thiomersal and other organomercurials as preservative in biopharmaceuticals (CPMP/BWP/1009/97) to the Safety Working Party and the CPMP respectively.

The CPMP's Safety Working Party examined safety concerns related to the use of thiomersal at their February 1998 meeting and made preliminary recommendations to the CPMP (CPMP/SWP/175/98). On 22 April 1998 the CPMP, having considered the report from the SWP, agreed on a Concept Paper on Thiomersal (CPMP/767/98) which outlined a multidisciplinary action plan to evaluate the benefit/risk of medicinal products containing thiomersal.

In order to evaluate Thiomersal containing medicinal products from the quality and safety viewpoint specific questions were put to the committee's working parties: Quality Working Party (QWP), Biotechnology Working Party (BWP), Safety Working Party (SWP), and Pharmacovigilance Working Party (PhVWP).

On 19 October 1998 and 14 December 1998 multi-disciplinary meetings were held with representatives from each of above-mentioned working parties in order to discuss the risks and formulate recommendations for the CPMP. A meeting with Interested Parties (European Pharmacopoeia, WHO, FDA, and relevant manufacturers organisations) was held on 19 April 1999 to discuss the recommendations of the CPMP Working Document.

Toxicity

The toxicity profile of ethylmercury would appear to be similar to that of methylmercury. Therefore, data on methylmercury have been used in the assessment of risks associated with ethylmercury.

The main causes of concern with thiomersal are the induction of allergic reactions and due to the presence of ethylmercury, the potential risks of neurotoxicity. In non-pregnant adults, a Permissible Total Weekly Intake (PTWI) of 200 µg methylmercury has been recommended by the WHO [1](1990). At present, there is no international recommendation for a maximal intake in infants. Based on the WHO recommended PTWI and a documented higher sensitivity of fetuses and infants due to the vulnerability of the developing brain, the intake of methyl mercury in infants may exceed that which could be considered as safe.

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[1] WHO, Methylmercury, International Programme on Chemical Safety, Environmental Health Criteria 101, Geneva, 1990.

preservative used should be provided. (see CPMP Guideline CPMP/CVMP/QWP/115/95 "Note for Guidance on Inclusion of Antioxidants and Antimicrobial Preservatives in Medicinal Products").

- **Vaccines**

The fact that the target population for vaccines in primary immunisation schedules is a healthy one and in view of the demonstrated risk of sensitisation and the potential risk of neurotoxicity to infants and toddlers the group recognised that there was a greater burden to ensure that these otherwise healthy infants/toddlers are not subjected to such unnecessary risks (see recommendations below).

Conclusion

On the basis of the safety data available the group concluded that thiomersal should not be banned from medicinal products. However, taking into account the identified and theoretical risks of thiomersal and other mercurial containing preservatives, precautionary measures (as outlined below) should be considered

Ideally, the development of preservative-free formulations with strict adherence to the principles of GMP is considered to be the most desirable alternative.

However, the use of a preservative in certain medicinal products (e.g multidose preparations) is justified on public health grounds. The replacement of organomercurial compounds in these preparations should be carefully assessed taking into account the risk/benefit of the mercurial based preservative versus the alternatives. In order to do this the CPMP will continue to work with the relevant international bodies (European Pharmacopoeia, WHO, FDA) and the relevant product manufacturing bodies.

Recommendations

The group considered that it would be prudent to recommend the following precautionary measures:

- The presence of thiomersal (and other preservatives) in the composition of a medicinal product should be stated on the label.
- Where thiomersal or other preservatives are either added to a medicinal product or are used in the manufacturing process and are present in the final formulation in small but detectable amounts, the SPC and PL should contain information regarding the risk of sensitisation in relation to thiomersal and other preservatives.

  The PhVWP should draw up a European class warning on sensitisation for the SPC and PL of such products.
- For Immunoglobulins and eye/nasal preparations no further action is deemed necessary at this time.

  For vaccination in infants and toddlers the use of vaccines without thiomersal and other mercurial containing preservatives should be encouraged. In the interests of public health and in order not to jeopardize vaccine supplies and immunisation programs, the CPMP will continue to work with WHO, European Pharmacopoeia, FDA and vaccine manufacturers to reduce or eliminate where possible organomercurial preservatives in vaccines.

  The BWP should prepare a concept paper and then draft guidance to assist manufacturers in reformulating vaccines to reduce or eliminate organomercurial preservatives.

Please see Steve Hundley's attached review of the published pharm/tox data on thimerosal and methyl mercury. My only additional comment is that a GLP repro tox study with thimerosal might be useful. Also, on the question of sensitization studies, althought the murine local lymph node assay is alleged to be insensitive to metallic compounds, my hunch is this problem has been exaggerated and the LLNA might be appropriate for hypersensitivity assessment.

-Ken

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October 15,1998

To: Kenneth Hastings, Dr. P.H
Pharmacology Team Leader, HFD-590

From: Stephen Hundley, Ph.D.
Pharmacologist, HFD-590

Re: Thimerosal Toxicity Review

THIMEROSAL REVIEW

Thimerosal is currently used as a bacteriostatic agent in vaccine pro
influenza vaccines. The thimerosal concentration in these products i
(100⊣ g/ml) and injection volumes range from 0.5 to 1.0 ml (single im
vaccination for children includes three separate injections spread ov

Chemically, thimerosal is [(o-carboxy phenyl)thio] ethyl mercury and
thimerosal is used in vaccine formulations. Thimerosal degrades in s
of oxygen yielding thiosalicylate and ethyl mercury. Improper storag
vaccination product results in measurable degradation. The extent an
degradation under physiological conditions was not addressed in the a
published literature. The extent to which thimerosal was metabolized
animals or humans was also not determined in the referenced literatur

Based upon analogy to methyl mercury, the toxicity of ethyl mercury s
intact thimerosal or thiosaliclylate. Assuming complete cleavage of
50 ⊣ g of thimerosal following im dosing, the maximum amount of ethyl
released is approximately 28.3 ⊣ g or 0.12⊣ mole.

Thimerosal Toxicity

EXHIBIT
13

thimerosal-protein conjugate then subsequently challenged with the an adhered to contact lenses placed into each eye of rabbits on test. S ocular inflammation characterized by an influx of polymorphonuclear l anterior chamber and ocular tissue. No response was exhibited by non Multiple days of exposure to sensitized rabbits resulted in lymphoid lymphocytes, macrophages, and eosinophils with lower levels of neutro rabbits and rats, thimerosal was also positive in a guinea pig sentiz

Retrospective analysis of human patch tests of possible contact-sensi small percentage of cross-reactivity to thimerosal. Several literatu studies were identified with the range of percent positive thimerosal to more than 25% (10, 11, 12,13,14). In one of these studies, half a positive patch test to thimerosal also had postive patch test respo

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(10). However, there were only 55 subjects in this study and some of thimerosal may have been irritation rather than hypersensitivity.

The largest retrospective patch test study involved 2461 patients sus allergic response (11). Only 32 subjects in this group (1.3%) exhibi response to thimerosal. The authors concluded thimerosal hypersensit occurrance especially for vaccines administered im or subcutaneously. with contact dermatitis suggested higher percentages exhibited hypers patch tests than the adult population (12 & 13). As with other retro there was difficulty distinguishing between an allergic or irritation memory lymphocyte test was conducted on blood from patients with clin suspected metal intolerance (14). Thimerosal was included in the tes approximately 7% of the test group responded to thimerosal with a sti greater. The memory lymphocyte immunostimulation assay was well def citation, however, there was no definition of how the stimulation ind

The collection of animal and human studies indicated some degree of t with thimerosal. However, these literature articles lend themselves that is less than the level afforded by a complete report in an FDA s of the literature articles characterized the purity or extent of degr each study. It is crucial to know the extent to which thimerosal deg thiosalicylic acid prior to exposure to laboratory animals or humans.

Methyl Mercury Toxicity

The literature search did not locate published articles that examined in laboratory animals or human subjects. The closest analogy is meth Human toxicity to methyl mercury is well established and includes neu toxicity and genetic toxicity appearing as chromosomal aberrations. mercury toxicity include parathesia, ataxia, neurasthenia, vision and with 2 mg methyl mercury/kg body weight (19). Alterations in Nerve G concentrations in brains from juvenile rats were observed following i exposures to methyl mercury (20). The pregnant dams were maintained mg methyl mercury/kg feed during gestation through lactation. Based rats are not as sensitive to the neurological effects of methyl mercu monkeys.

Reproductive and developmental effects of methyl mercury were evaluat in mice (21,22,23,24). Pregnant mice dosed orally with 25 or 12.5 mg weight on Day 12 of gestation had fetuses with cleft palates on Day 1 for cleft palates was 100 percent at the 25 mg/kg dose level. Dead an resulted from the 25 mg/kg dose level. Pregnant mice dosed over a ra levels (3.6 to 27 mg/kg) on Day 9, 12, or 15 of gestation resulted in dose levels of 12 mg/kg and higher (22). The effects were more prono mercury dose was administered on Day 9 of gestation. Pregnant mice d

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Day 5 of gestation with 10 or 20 mg/kg levels of methyl mercury resul abnormal fetuses, higher fetal mortality, reduced number of implants viable fetuses (23). There were no indications of embryo or fetal to of 2.5 and 5.0 mg/kg. In a separate study, pregnant mice dosed oral gestation with methyl mercury levels of 3 mg/kg and higher resulted i at each dose level (24) with an incidence rate of 27% at the lowest d resorptions were observed at the two highest methyl mercury dose leve administration of N-acetyl cysteine provided a measure of protection toxicity from methyl mercury.

The reproductive effects of methyl mercury in female monkeys (Macaca evaluated by daily oral doses of 50 or 90 ┤g/kg through four menstrua 124 days) prior to mating (25). Effects on reproduction (spontaneous nonconception rates) were greater for the 90 ┤g/kg dose-group compare These effects were not different from control rates for the 50 ┤g/kg mercury levels associated with reproductive failure ranged from 1.9 t clinical signs of mercury-induced neurotoxicity were observed in the following determination of reproductive failure or success.

Testicular effects of methyl mercury in male monkeys (Macaca fascicul a 20-week dosing period with daily oral methyl mercury doses of 50 or semen samples revealed decreased sperm motility and speed, and tail d dose-group. No effects were observed in semen samples from the 50 ┤g Testicular biopsies were taken at the termination of methyl mercury d histopathological effects were observed at either dose level. No clin observed during and following dosing. Male mice were also sensitive methyl mercury dosed im with daily 20 ┤g amounts (approximately 0.8 m 30 days (27). Sperm motility and count were reduced compared to zero abnormal sperm morphology and low serum testosterone were also observ

for methyl mercury is equivalent to the maximum possible amount of et
released from a single injection of a vaccine product. Blood or tis
single vaccination containing 50 µg of thimerosal would probably not
quantitatively from mercury levels resulting from acceptable daily ex

Embryo and fetal lethality resulted from ip administration of 2 mg (7
thimerosal to pregnant rats on Day 6 through 18 of gestation. The do
thimerosal to a 67 kg person is approximately 0.75 µg/kg body weight
lower based on a mg/kg basis. The difference is approximately 780-fo
body surface area. The potential for thimerosal to cause development
toxicological effects from a single dose of a vaccination product is
comparison.

The reviewed animal studies for methyl mercury demonstrated that the
that could be liberated from thimerosal is insufficient to produce ne
reproductive toxicity. The most sensitive toxicity index for methyl
exposed developing fetuses continuing to juvenile age monkeys with ex
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from approximately 0.11 to 0.32 µmole/kg as either no effect or minim
comparison, the ethyl mercury dose level for a single injection to a
1.8 nmole/kg [approximately 61-fold lower on a mg/kg basis]. The oth
that were reviewed resulted from much higher methyl mercury dose leve
was testicular toxicity at 5 and 10 µg/kg reported from one laborator
strain of rats. However, the testicular effects were not as severe i
dose levels (0.1 and 0.5 mg/kg). There were no other reports of test
levels as low as 10 µg/kg. If the effects observed at the 10 µg/kg d
levels 10 or 100 times higher should have resulted in an absence of s
rats. There were no reports in this search of scientific literature
methyl mercury exposure.

A substantial body of human epidemiological data suggest thimerosal i
small percentage of people exposed in one manner or another to thimer
retrospective analyses and did not define the past thimerosal exposur
positive responses may have resulted from previous exposure to thimer
products where the potential for release of ethyl mercury from thimer
from im or sc injecitons of a vaccination product. In addition, the
the referenced literature indicated possible errors in distinguishing
irritation responses in the human patch tests.

There are several types of data that can assist in defining the actua
presence of thimerosal in vaccination products.

- Determine blood mercury levels [organic and inorganic mercury] i
  prior to and immediately after vaccination. Can an elevation in
  determined following vaccination?

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Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Vaccines Research and Review

Review under the FDAMA Section 413(c)

Thimerosal in Childhood Vaccines: A Reassessment

Summary:

In response to the Food and Drug Modernization Act of 1997 (FDAMA), Section 413(c) requiring study of the health effects of mercury in drugs, the Center for Biologics Evaluation and Research (CBER) conducted a risk assessment of the use of thimerosal, a mercury-containing preservative, in childhood vaccines.

The risk assessment consisted of hazard identification, dose-response assessment, exposure assessment, and risk characterization. The literature was reviewed to identify known toxicity of thimerosal, ethylmercury (a metabolite of thimerosal) and methylmercury (a similar organic mercury compound) and to determine the doses at which toxicity occurs. Maximal potential exposure to mercury from vaccines was calculated for children at age 6 months and 2 years, under the U.S childhood immunization schedule, and compared to the limits for mercury exposure developed by the Environmental Protection Agency (EPA), Agency for Toxic Substance and Disease Registry (ATSDR), the FDA, and the World Health Organization (WHO).

Delayed-type hypersensitivity reactions from thimerosal exposure are well recognized. Identified acute toxicity from inadvertent high dose exposure to thimerosal includes neuro- and nephrotoxicity. Limited data on toxicity from low dose exposures to ethylmercury are available, but toxicity may be similar to that of methylmercury. Chronic, low dose methylmercury exposure may cause subtle neurological abnormalities. Depending on the vaccine schedule and formulation, cumulative exposure of infants to mercury from thimerosal during the first 6 months of life may exceed EPA guidelines, but not the ATSDR, FDA, and WHO recommendations.

Our review revealed no evidence of harm caused by doses of thimerosal in vaccines, except for local hypersensitivity reactions. However, some infants may be exposed to cumulative levels of mercury during the first six months of life that exceed EPA recommendations. Exposure of infants to mercury in vaccines can be reduced by using products formulated without thimerosal as a preservative.

Introduction

The FDA Modernization Act of 1997 Section 413(c)[1] calls for the study of human health effects of elemental, organic, or inorganic mercury found in drugs and dietary supplements. Specifically, the Act requires evaluation of the "adverse effects on health of children and other sensitive populations from exposure to...mercury". Thimerosal is an organic mercurial compound included as a preservative in biological products since the 1930's. It is the most widely used preservative in vaccines, found in over 30 U.S. licensed and currently marketed vaccines, in concentrations of 0.003 to 0.01%. In response to FDAMA Section 413(c), CBER conducted a risk assessment of thimerosal in childhood vaccines, as this constitutes the largest cumulative exposure (in µg/kg body weight) to mercury from any biological product.

FDA regulations require that preservatives be present in multidose vials of vaccines, with the exception of certain live viral vaccines, to prevent bacterial and fungal contamination.[2] Preservatives are not required for products formulated in single dose vials. Multidose vials are preferred by some physicians and health clinics because they are often less expensive per vaccine dose and require less storage space. As a preservative, thimerosal may be added at the end of the production process to the bulk or final container, or it may be added to the diluent of a lyophilized vaccine. In addition to its prominent role as a preservative, thimerosal is used as an inactivating agent in the manufacture of certain vaccines (e.g., whole cell pertussis vaccines and some acellular pertussis products) and as a bacteriostatic agent during the production process of other vaccines (e.g., influenza vaccines).[3] Uses other than as a preservative, however, contribute little to the final concentration of thimerosal in vaccines (at most 2-3 µg thimerosal/ml), with limits of detection of less than 0.2 µg thimerosal/ml.[4]

CBER/OVRR Review under FDAMA Section 413(c)

Formal FDA review of thimerosal use in biological products, including vaccines, last occurred in 1976. This review evaluated exposure to thimerosal from biological products using the 1974 American Academy of Pediatrics "Red Book" immunization schedule and concluded that, with the exception of long term immune globulin replacement therapy, "no dangerous quantity of mercury is likely to be received from biologic products in a lifetime."[5] Thimerosal is no longer used as a preservative in U.S. licensed immune globulin products such as intravenous immune globulin, hepatitis B immune globulin (HBIG), varicella immune globulin (VZIG), with the exception of a few immune globulin preparations for intramuscular administration and some Rho (D) immune globulins. Reassessment of the risks from thimerosal in vaccines is appropriate in light of advances in the understanding of the human health effects of exposure to mercury,[6,7,8] as well as the increased number of vaccines recommended for routine use in children.

Methods

Our risk assessment of thimerosal in childhood vaccines, adapted from the paradigm outlined by the National Research Council,[9] consisted of hazard identification, dose-response assessment, exposure assessment, and risk characterization. The population studied was infants and young children because of their small body size, developing brain, and exposure to vaccines containing thimerosal.

We reviewed the medical literature to identify the known risks of thimerosal and related organic mercury compounds by querying MEDLINE and TOXLINE databases, using the MESH terms "thimerosal", "thiomersal", "merthiolate", "mercury", "ethylmercury", "methylmercury", "immunization", "vaccine", and "preservative". Additional articles were obtained from the reference lists acquired during the initial search and from colleagues. The Vaccine Adverse Event Reporting System (VAERS), a national passive surveillance system maintained by the FDA and CDC,[10] was queried for reports of adverse events associated with thimerosal. We examined dose-response relationships and exposure limits recommended by various agencies for methylmercury, a related organic mercurial compound. To simplify the comparison between ethyl- and methylmercury, we calculated the amount of mercury by weight for both compounds. We tabulated the mercury content of all U.S. licensed vaccines, determined the range of exposures to mercury that a child could receive under the recommended U.S. childhood immunization schedule, and characterized the potential risk to infants. Given the limitations of available data pertaining to thimerosal toxicity, we did not attempt a quantitative risk characterization.

Results

Hazard identification

To identify hazards of thimerosal, we reviewed reports of toxicity in animals and humans. Because no controlled studies have been conducted to examine low dose thimerosal toxicity in humans, the reported toxicity of methylmercury, a related organic mercury compound, was evaluated.

Animal Studies

Limited animal studies have examined the toxicity of thimerosal or ethylmercury. Low doses of thimerosal equivalent to ethylmercury doses of either 1 or 6 μg/kg/day in adult squirrel monkeys were converted to inorganic mercury, with high levels detected in the kidney and lower levels found in the brain.[11] Histopathological changes were not observed in either the kidney or brain.

Prior to the marketing of thimerosal as a preservative in 1931, high dose toxicity studies were conducted in rabbits, rats, mice, dogs and guinea pigs.[12] Rabbits, rats, and mice received intravenous injections of 1% solution with observation periods limited to 7 days; the use of control animals was not reported.

The maximum tolerated doses were reported as 20 mg/kg (rabbits) and 45mg/kg (rats). For rabbits, the pathology of fatal cases was described as "essentially that of mercurial poisoning, including kidney and intestinal lesions." Four dogs received 2 mg/kg of 1% solution every third day for 12 doses. Autopsies performed seven days after completion found "only minor microscopic tissue changes." Immediately following intraperitoneal injections of 1/1000 (0.1%) solution, guinea pigs demonstrated evidence of severe pain. "Fairly pronounced" congestion and hemorrhage in the visceral, parietal and omental peritoneum was observed when animals were sacrificed and examined 1-2 days after injection. The authors reported that "no abnormal pain responses" were seen in guinea pigs injected with dilutions of 1/4000 and 1/8000.[12]

In a more recent carcinogenicity and toxicity study of preservatives in vaccines, Fischer rats were subcutaneously injected twice-weekly with thimerosal at doses ranging from 30 to 1000 μg /kg for 1 year.[13] Control rats were either untreated (negative control), or treated with nickel which is known to induce local inflammatory reactions (positive control). Animals were weighed weekly and autopsied at either 12 or 18 months after initial injection. All animals with spontaneous deaths, moribund, or with gross organ pathology had organs examined histologically. The thimerosal-treated rats had a dose-dependent increase in the incidence of bronchopneumonia, compared with rats receiving other preservatives or controls, with 60% of the thimerosal-treated animals demonstrating unspecified histopathologic changes at the highest dose, compared with 13% of untreated controls. The death rate for the thimerosal-treated animals paralleled that of other preservatives and controls leading the authors to conclude "the damage was slight, continuous, and perhaps cumulative." In addition, animals receiving thimerosal at the highest dose levels over the 12 months period demonstrated on average a 10% (range 5-14%) retardation of weight gain when compared with controls. Histopathology of the brain and kidney in thimerosal-treated animals was not reported. Quantitative data were compiled only for the highest dose levels; at lower doses the retardation of weight gains was reported to be "less significant".[13]

Human Studies

Allergy to thimerosal is well described in the clinical literature, primarily in the form of delayed-type hypersensitivity.[14] Some authors postulate that the thiosalicylate component is the major determinant of allergic reactions.[15] The clinical importance of the high prevalence of thimerosal sensitivity detected by patch testing remains controversial. Some investigators feel that it is of little significance,[16,17] while others suggest it is important enough to require removal from pharmaceutical products.[13,18,19]

Our search did not locate any reports of formal human toxicity studies performed prior to initial marketing of thimerosal. The earliest report of thimerosal use in humans was found in a 1931 article by Powell and Jamieson.[12] In this report of clinical use by another investigator, 22 individuals received 1% solution of thimerosal intravenously for unspecified therapeutic reasons. Subjects received up to 10 mg thimerosal/kg with no reported toxic effects, although 2 subjects demonstrated phlebitis or sloughing of skin after local infiltration. Of note, this study was not specifically designed to examine toxicity; 7 of 22 subjects were observed for only one day, the specific clinical assessments were not described, and no laboratory studies were reported.

Clinical cases of accidental and intentional acute poisonings with very high doses of thimerosal, while rare, point to the severest forms of toxicity. Several cases of acute mercury poisoning from thimerosal-containing products were found in the medical literature. These reports included the administration of immune globulin[20] (gamma globulin) and hepatitis B immune globulin,[21] choramphenicol formulated with 1000 times the proper dose of thimerosal as a preservative,[22] thimerosal ear irrigation in a child with tympanostomy tubes,[23] thimerosal treatment of omphaloceles in infants,[24] and a suicide attempt with thimerosal.[25] Total doses of thimerosal administered in these reports of acute toxicity ranged from approximately 3 mg/kg to several hundred mg/kg. These studies reported local necrosis, acute hemolysis, disseminated intravascular coagulation, acute renal tubular necrosis, and central nervous system injury including obtundation, coma, and death.

Methylmercury Toxicity Studies

We did not find any reports of toxicity following low dose exposure to thimerosal in humans in the medical literature. However, available data suggest that the toxicity of ethylmercury, the thimerosal metabolite, and methylmercury may be comparable. Limited animal data are available on the comparative toxicity of ethyl- and methylmercury; only one animal study directly comparing the toxicity of these agents was found. Magos studied adult male and female rats administered 5 daily doses of equimolar concentrations (8.0 mg/kg) of ethyl- or methylmercury by gavage or 9.6 mg/kg ethylmercury.[26] Tissue distribution, the extent and severity of histological changes in the brain and kidney, and effects on coordination were assessed. Magos concluded that equimolar doses of ethylmercury were less neurotoxic than methylmercury, as measured by coordination disorders in treated rats and histopathologic changes in the dorsal root ganglia. However, increasing the dose of ethylmercury by 20% caused higher coordination disorder scores and significantly more damage to the dorsal root ganglion than in methylmercury treated rats. Renal damage was greater in rats receiving equimolar doses of ethylmercury compared to methylmercury.

In humans, high dose exposure to ethylmercury has resulted in toxicity similar to that of high dose exposure to methylmercury.[27] Because high dose exposure to ethylmercury from thimerosal results in toxicity comparable to that observed following high dose exposure to methylmercury, and because of the chemical similarity of the two compounds, it appears reasonable to consider toxicity of low doses of methylmercury and ethylmercury to be similar.[29,30]

Much of what is known about methylmercury toxicity comes from poisoning episodes in Japan[30] and Iraq,[31] as well as studies of populations with dietary exposure, primarily in the Seychelles[32] and Faroe Islands.[33] The toxicity of methylmercury was first recognized during the late 1950s and early 1960s with the consumption of contaminated fish in Minamata, Japan.[30] Epidemics of methylmercury poisoning also occurred in Iraq during the 1970s when seed grain treated with a methylmercury fungicide entered the food chain as bread.[31] Maternal methylmercury exposure in these epidemics was associated with neurological abnormalities, such as delays in motor function, among children exposed in utero.

Additional data from low dose exposure to methylmercury derived from studies of populations exposed in their diet are conflicting.[32,33] Studies from the Faroe Islands reported that subtle abnormalities (e.g., finger tapping delays), detectable by sophisticated neuropsychometric testing, were associated with methylmercury levels previously thought to be safe.[32] Studies in the Seychelles, evaluating more global developmental outcomes, did not reveal any correlation between abnormalities and mercury levels.[33]

Vaccine Adverse Event Reporting System

To identify any events reported as attributable to thimerosal in vaccines, we queried approximately 90,000 VAERS reports from 1990-1998 by searching text fields for "thimerosal", "thiomersal", "merthiolate", and "mercury". Forty-five reports were identified. The types of events reported and vaccines administered are shown in Tables 1 and 2. Of note, one report described an individual who experienced anaphylaxis following hepatitis B vaccine. When rechallenged with a similar but thimerosal-free product, anaphylaxis occurred again, implying thimerosal was not the causative agent. VAERS has several limitations, including lack of consistent diagnostic criteria, data acquired from a diverse group of voluntary reporters, underreporting, and the difficulty in determining whether a vaccine caused the adverse event reported.[10] A cause and effect relationship between the reported adverse events and thimerosal in vaccines cannot be established because of these limitations.

Summary of Hazard Identification

The only well established hazard of thimerosal at doses found in vaccines is delayed-type hypersensitivity reactions. At very high doses, the identified hazards of thimerosal are neuro- and nephrotoxicity. Methylmercury, a similar organic mercurial, has been associated in some studies with subtle neurodevelopmental abnormalities at low doses. Although the data are limited, similar toxicological profiles between ethylmercury and methylmercury suggest that neurotoxicity may also occur at low doses of thimerosal; however, such effects have not been reported.

Dose-Response Assessment

Guidelines for Safe Exposure to Methylmercury

Guidelines for safe exposure to methylmercury, based on dose-response analysis of exposures resulting in overt toxicity, were used to determine whether the mercury dose from vaccines approaches a level of concern. The U.S. Environmental Protection Agency (EPA),[7] U.S. Agency for Toxic Substances and Disease Registry (ATSDR),[34] the FDA,[35] and the World Health Organization (WHO)[36] have developed recommendations for limits of exposure to methylmercury in the diet. These range from 0.1 µg/kg body weight/day (EPA) to 0.47 µg/kg body weight/day (WHO)[*] and include varying safety margins. The range of recommendations results from differing emphasis placed on various primary data sources and the different purposes for these recommendations. All guidelines, however, fall within the same order of magnitude. A complete discussion of the how each agency reached its recommendations and the intended purpose is beyond the scope of this risk assessment. The interested reader is referred to a recent review.[8] Application of these guidelines to a female infant at the 5th, 50th and 95th percentile of weight between birth and 26 weeks,[37] the period during which most infant vaccines are given, resulted in calculated recommended limits of mercury exposure shown in Table 3. This assessment assumed that the toxicity and pharmacokinetics of ethylmercury are the same as methylmercury (which has not been established) and is based on the conservative assumption that the susceptibility of the infant to toxicity from organic mercurials is the same as that of the fetus. Calculations also assumed limited or no excretion in newborns.

Exposure Assessment

An exposure assessment was undertaken of the mercury content of vaccines included in the recommended U.S. childhood immunization schedule.[38] At the time of this review, childhood vaccines that might contain thimerosal as a preservative included single antigen hepatitis B vaccines; some diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccines; all diphtheria and tetanus toxoids and whole cell pertussis (DTP) vaccines; and some *Haemophilus influenzae* type b (Hib) vaccines. The total amount of

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[§] The WHO guideline is expressed as 3.3µg/kg body weight/week and has been converted to a daily dose for mercury by molecular weight was calculated for each vaccine in the infant schedule. For formulations containing thimerosal as a preservative, hepatitis B vaccine contains approximately 12.5 µg mercury per 0.5 ml dose, DTaP or DTP approximately 25 µg mercury, and Hib vaccine approximately 25 µg mercury. Depending on the particular vaccine formulation and schedule, an infant may receive a total mercury dose from vaccines as much as 187.5 µg during the first 6 months of life. In special populations, influenza vaccine may be administered at 6 months of age, which would increase the total dose to approximately 200 µg (Table 4). Thus, comparison with Table 3 shows that some infants may receive doses of mercury from vaccines that are in excess of EPA guidelines, but not the ATSDR, FDA, or WHO guidelines.

At the time of this risk assessment, vaccine formulations not containing thimerosal as a preservative were available for Hib (ActHIB® and HIBtiter® in single dose vials), DTaP (Infanrix®), and a combination Hib-hepatitis B vaccine (COMVAX®). Subsequently, two single dose formulations of preservative-free hepatitis B vaccine were approved by the FDA: on August 27, 1999 for Recombivax-HB®[39] and on March 28, 2000 for Engerix-B®. The Hib-hepatitis B combination vaccine (COMVAX®) is licensed for use in infants ≥ 6 weeks of age, born to mothers with low risk of hepatitis B. Vaccines that use thimerosal during the production process, but not as a preservative, contain less than 3 µg thimerosal/ml and, therefore, are not considered in this exposure assessment. With the currently available U.S. licensed vaccines, cumulative infant exposure to mercury from vaccines can be less than EPA recommended limits, under most circumstances. Under special circumstances the ACIP[40] and AAP[41] allow for accelerated schedules for infants, such as infants at risk of exposure to pertussis and for travelers. Administering vaccines

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purpose of comparison.

containing thimerosal as a preservative to these infants would result in exposure to more mercury per kilogram body weight over a shorter period of time.

Estimates of thimerosal exposure from vaccines among 85,000 children who receive health care in a large health maintenance organization in California indicate that approximately 25% of infants received ethylmercury from vaccines in excess of the EPA methylmercury guidelines by 6 months of age, but not in excess of the ATSDR, FDA, or WHO guidelines.[42] In addition, certain infants may be exposed to high levels of mercury from the diet or environment. These exposures should be added to those from vaccines in assessing the total exposure of infants to mercury. By the second year of life the larger body size of even the smallest children results in a calculated exposure which is less than the EPA, ATSDR, FDA, and WHO guidelines. (Table 5)

No human data are available regarding neurotoxicity from thimerosal containing vaccines. However, one recent study measured the change in total mercury blood levels in a small number of infants after hepatitis B vaccination. Following one dose of hepatitis B vaccine (approximately 12.5 µg of mercury) given within 3 days of birth, mean mercury blood levels increased from 0.54 to 7.36 µg/L (range 1.3-23.6) in 15 pre-term infants with a mean body weight of 748 g; and from 0.04 to 2.24 µg/L (range 1.4- 2.9) in 5 term infants with a mean body weight of 3.59 kg.[43] This study demonstrated that a birth dose of hepatitis B vaccine can measurably increase infant mercury blood levels. These levels are not generally considered acutely toxic; however, the long-term effects on neurodevelopment from this level of exposure have not been studied.

Discussion

Risk Characterization

No evidence of harm has been demonstrated at doses of thimerosal found in vaccines, except for local hypersensitivity reactions. Available clinical data, however, do not address the potential for subtle effects in infants. A pre-licensure study of intentionally administered high dose thimerosal,[12] cited as demonstrating its safety,[5] may not be directly relevant to the issue of thimerosal in childhood vaccines. This study was performed over 60 years ago when different safety standards existed; the study was not designed to look for chronic toxicity, did not include pharmacokinetics, and did not enroll infants. Case reports of neurotoxicity and renal toxicity from thimerosal in humans were found only at doses >100 times that found in vaccines. Our analysis concluded that the use of thimerosal as a preservative in vaccines might result in intake of mercury during the first six months of life that exceeds the EPA, but not the ATSDR, FDA, or WHO guidelines for methylmercury intake. The clinical significance of this conclusion is not currently known. The EPA guidelines contain as much as a ten-fold safety factor. Such guidelines are meant to be starting points for evaluation of mercury exposure, and should not be viewed as absolute levels above which toxicity can be expected to occur.[8]

Precisely identifying the risk from thimerosal in vaccines is problematic because of gaps in knowledge of its toxicity. This risk assessment extrapolates the toxicity from methylmercury exposure to that of ethylmercury from thimerosal in vaccines. This extrapolation has several limitations. The comparative toxicity of ethyl- and methylmercury has not been well characterized. Moreover, the metabolism and elimination of ethylmercury compared with methylmercury, and the effect of intermittent intramuscular doses of thimerosal from vaccines compared with chronic low dose oral exposure to methylmercury, has not been studied. Several of the guidelines for methylmercury exposure are based on studies of fetal outcomes after in utero exposures from maternal ingestion of methylmercury-contaminated food. The susceptibility of the infant compared with the fetus to adverse effects from organic mercurials is not known. While acknowledging the limitations of available data and the uncertainties inherent in our risk assessment, we cannot exclude the possibility of subtle neurodevelopmental abnormalities from the cumulative exposure to thimerosal in vaccines.

Options Regarding Thimerosal as a Preservative in Childhood Vaccines

Three general options exist regarding the use of thimerosal as a preservative in childhood vaccines: maintaining current vaccine formulations, eliminating thimerosal from vaccines, or reducing exposure to thimerosal. Reduction in exposure to thimerosal from vaccines is merited given the goal of reducing human exposure to mercury from all sources, the availability of alternatives to thimerosal as preservative in vaccines, and the potential risk to infants.

Complete elimination of thimerosal from all vaccines in the near future is not likely. Reformulation of vaccines that include thimerosal in the production process will require further product characterization, and perhaps clinical studies, to establish safety, purity, potency, stability, and efficacy.[3] For some vaccines, removal of thimerosal may alter the antigenic structure and thus the immune response. If a new preservative is to replace thimerosal, the safety and efficacy of the alternative must first be established.[44]

Several approaches are available to reduce exposure of children to thimerosal. Clinicians may select existing products not containing thimerosal. Reformulation of vaccines in single dose vials may eliminate the need for a preservative. For some vaccines, such as the recently approved single antigen hepatitis B vaccine (Recombivax®), reformulation in single dose vials could be accomplished rapidly because the vaccine was already formulated and stored in bulk without thimerosal as a preservative. While transition to single dose vials may be an option in the U.S., multidose vials containing thimerosal remain, at present, an important component of immunization programs in developing countries because of their reduced cost and storage requirements. In such settings, the WHO has determined that the benefits of vaccination and the risk of microbial contamination of multidose vials outweigh the theoretical risks of thimerosal in vaccines.[45,46]

Several new vaccines, formulated without thimerosal as a preservative, are under development by vaccine manufacturers, including combination products. If licensed, these vaccines would greatly expand options available to clinicians. Another possibility to reduce thimerosal exposure is to reformulate vaccines with reduced amounts of thimerosal that still have a preservative effect. In the long term, preservative-free products formulated in single dose vials, substitution of alternative preservatives, or implementation of new vaccine technologies such as combination, mucosal, trancutaneous, and DNA vaccines may further reduce or eliminate the need for thimerosal as a preservative in childhood vaccines.

Actions Taken to Date

On July 1, 1999, the FDA sent a letter to manufacturers of vaccines requesting their plans to remove thimerosal from U.S. licensed vaccines, or alternatively, an explanation for continued use of thimerosal as a vaccine preservative.[47] In July 1999, the AAP and the PHS issued a joint statement[48] and the AAP released an interim report to clinicians[49] recommending that thimerosal be removed from vaccines as soon as possible, while maintaining efforts to ensure high vaccination levels. The joint statement included a commitment by the FDA to expedite the review of manufacturers' proposals to remove thimerosal as a preservative from vaccines. One recommendation arising from these reports included deferral of hepatitis B vaccination until 2 to 6 months of age for infants born to low risk mothers. With the approval of a single antigen thimerosal-free hepatitis B vaccine in August 1999, the Advisory Committee on Immunization Practices (ACIP) recommended that the birth dose of hepatitis B vaccine be resumed, and that infants under 2 months of age be given preference for thimerosal-free products where supplies are limited. In November 1999, the ACIP reaffirmed these recommendations.[50] Additional proposals by manufacturers to remove thimerosal as a preservative from vaccines are under review by the FDA. In August 1999 the Centers for Disease Control and Prevention and the National Vaccine Advisory Committee sponsored an open public forum on Thimerosal in Vaccines, with representatives from Public Health Service Agencies, other U.S. government agencies, academia, industry, and the international vaccine community, to examine relevant issues.

Research needs

Data are lacking regarding the biotransformation and pharmacokinetics of thimerosal and its derivatives following intramuscular injection in humans and animal models. Moreover, insufficient information is available to adequately assess the potential for neurodevelopmental, renal, immunologic, and reproductive toxicity of thimerosal. Limited data exist on the mercury exposure of infants from vaccines, and no observational studies have been done in humans to assess any possible effects of thimerosal exposure on neurodevelopment, renal, and immunological function. Thimerosal is unlikely to be eliminated from all vaccines in the near future, and studies are needed to address these gaps to provide a more precise characterization of the potential risk from thimerosal in vaccines.

Conclusion

Our review revealed no evidence of harm caused by doses of thimerosal found in vaccines, except for local hypersensitivity reactions. Vaccines containing thimerosal as a preservative may expose infants to cumulative mercury at levels that exceed EPA recommendations during the first six months of life. The clinical significance of this conclusion is not currently known; EPA guidelines contain as much as a ten-fold safety factor and such guidelines are meant to be starting points for the evaluation of mercury exposure. However, reducing exposure to thimerosal from vaccines is merited given the goal of reducing human exposure to mercury from all sources, the availability of alternatives to thimerosal as preservative in vaccines, and the desirability of ensuring the highest possible level of public confidence in the safety of vaccines.

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Table 1: Reports to VAERS Attributed by Reporter to Thimerosal[§] by Vaccine Type

Hepatitis B	28
Influenza	10
Tetanus/Diphtheria	3
Haemophilus influenzae type b (HIB)	1
DTaP	1
DTP/HIB (TETRAMUNE)	1
DTP and HIB (Concurrent administration)	1

[§] Thimerosal, thiomersal, merthiolate, or mercury

Table 2: Types of Events Attributed by Reporter[§] to Thimerosal

Injection site reaction	13
Rash	9
Urticaria**	8
Edema†	5
Flu-like syndrome/joint aches¥	4
Anaphylaxis‡	1
"Severe allergic reaction"#	1
Wheezing**	1
Stridor	1
Malaise/agitation	1
Reaction not specified	2

[§]Thimerosal, thiomersal, merthiolate, or mercury

Note: Only one report (angioneurotic edema) required hospitalization. Most others reported doctor visits or emergency room visits.

**One report involved a patient with urticaria and wheezing, onset after vaccination not specified.

†One report of edema required hospitalization for angioneurotic edema, two reports of facial edema, one report of eyelid edema, one peripheral edema.

¥One patient also reported fever to 102°F.

#Not otherwise specified.

‡Patient had placebo-controlled rechallenge with similar vaccine formulated without thimerosal and had anaphylaxis; thus, anaphylaxis *not* thought to be due to thimerosal.

Table 3: Calculated Exposure Limits for Mercury, Using Various Agency Guidelines for Exposure to Methylmercury, in Infants ≤ 6 Months of Age by Percentile Body Weight

Agency	**Percentile Body Weight**		
	5th	**50th**	**95th**
EPA	65 μg	89 μg	106 μg
ATSDR	194 μg	266 μg	319 μg
FDA	259 μg	354 μg	425 μg
WHO	305 μg	417 μg	501 μg

- Calculated Exposure Limit = dose/kg body weight/week X average weight X 26 weeks X 0.932 (mercury molecular weight/ methylmercury molecular weight); e.g., EPA calculated exposure limit = 0.7 μg/kg body weight/week X 26 weeks X (2.36 kg + 5.25 kg)/2 X 0.932 = 65 μg.
- Assumes average of 5th, 50th, and 95th% weight for females at birth (2.36 kg, 3.23 kg, 3.81 kg) and 6 months (5.25 kg, 7.21 kg, 8.73 kg) = 3.81 kg, 5.22 kg, 6.27 kg. Females were selected because their smaller body weight makes them more susceptible than males.
- Recommended limits on methylmercury exposure:

  EPA: 0.1 μg/kg body weight/day; ATSDR: 0.3 μg/kg body weight/day;

  FDA: 0.4 μg/kg body weight/day; WHO 3.3 μg/kg body weight/week.

  For calculations, daily limits multiplied by 7 to obtain weekly limits.

CBER/OVRR Review under FDAMA Section 413(c)

Table 4 - Exposure to Mercury from Vaccines in U.S. Infants (≤ 6 months)

Vaccine	**Minimum Mercury Dose**	**Maximum Mercury Dose**
DTaP x 3	0 µg	75 µg
Hib x 3	0 µg	75 µg
Hepatitis B x 3	0 µg	37.5 µg
Hib-Hepatitis B x 2	0 µg	NA
[Influenza] [ξ] (selected populations)	[12.5 µg]	[12.5 µg]
Total	**[12.5 µg]**	**187.5 µg [200 µg]**

[ξ] Brackets denote dose of mercury if influenza vaccine is administered.

Thimerosal is 49.6% mercury by weight; e.g., 0.005% thimerosal concentration is equivalent to 50 µg thimerosal/1.0 ml or 25 µg thimerosal/0.5 ml and results in approximately 12.5 µg mercury/0.5 ml dose

Note: These calculations do not include mercury exposures from sources other than vaccines.

NA: Not applicable

Meeting Memorandum

MATERNAL IMMUNIZATION WORKING GROUP

Date: 10/13/98 **Time:** 8:30 a.m. - 10:00 a.m.

Participants: M. Gruber, M.C. Hardegree, M. Serabian, N. Baylor, B. Sheets, K. Midthun, J. Clifford, L. Falk, K. Goldenthal, H. Jolson (CDER), K. Hastings (CDER)

Subject: Pregnancy registries;
Discussion of point paper: "Reproductive toxicity study requirements for vaccines"

Presentation by Dr. Jolson:

Dr. Heidi Jolson (Division Director of Antiviral Drug products, CDER; Chair of the pregnancy registry & Guidance working group)presented an overview of pregnancy registry initiatives:

The pregnancy labeling task force(PLT)is an agency-wide initiative charged with reformatting the pregnancy label section. There are two groups reporting to the pregnancy labeling task force, the preclinical working group and the clinical working group, i.e., the pregnancy registry working group. The purpose of this working group is to develop recommendations for incorporating the results of pregnancy registry data in the "Pregnancy" section of the package insert. The group is developing an internal document for clinical reviewers to assist the reviewer in interpreting pregnancy outcome data as well as a pregnancy registries guidance document aimed at industry. In addition, a reviewer training course is offered that is designed to introduce the reviewer to issues that commonly arise in the course of reviewing human pregnancy outcome data.

1. Pregnancy Registries Initiatives

There are currently numerous problems with regard to the pregnancy related sections, i.e., pregnancy category system A, B, C, of a package insert for a marketed drug: a) There is in general a lack of data form human clinical studies in this section, because new drugs are infrequently studied in pregnant women, b) only if severe adverse outcomes are observed (severe

PENGAD-Bayonne, N. J.
EXHIBIT
15

malformations, developmental anomalies) information will be included in the pregnancy section (example thalidomide), c) it is difficult to extrapolate the results from animal pre-clinical reproductive toxicity studies to humans, and d) there is often a lack of sponsor incentive to develop relevant information.

The question was raised what the CDER requirements for pre-clinical studies are and for what products they apply, i.e., would they be required for products that are not administered more than 3-4 time in a lifetime of the subject. Dr. Hastings explained that Segment II repro-tox studies are generally obtained prior to proceeding to Phase 2 studies and that full repro-tox studies (all segments) should be completed prior to initiating Phase 3 clinical trials. These studies are usually required for drugs that are given to treat chronic conditions, i.e. repeatedly administered drugs, however these type of studies have also been performed for products that are given infrequently. CDER's experience is that sponsors usually conduct reproductive toxicity studies because of liability issues. CDER has more problems to get sponsors to conduct chronic carcinogenicity studies requiring extended periods of time. The point was made that vaccine manufacturers whose products are regulated by OVRR are often reluctant to perform preclinical repro-tox studies, because these products usually are not administered for extended periods of time. However, the argument can be made that even if the product is given infrequently it can trigger an immune response, that may have long lasting consequences on the organisms justifying the pre-clinical repro-tox evaluation of such products.

Pregnancy registries are prospectively defined, observational studies in which exposed women are recruited and followed to determine the outcome of any known pregnancy. Pregnancy registries are not clinical trials but rather of epidemiological nature. Sponsors should determine the outcome of each pregnancy and calculate the rate of any complications and fetal abnormalities compared to rates observed in unexposed women. It was discussed that the comparisons performed are likely not perfect and there is a certain bias, since it may be difficult to adjust for potential confounders such as population, geographical areas, age, race etc. This was acknowledged but it was stressed that he goal of any pregnancy registry is to achieve as good of a comparison as doable and to make an effort to adjust for maternal risk factors.

It was discussed that a certain "background noise" in terms of abnormalities and birth defects are expected. It is not really important that there is a certain percentage of background noise, but what the observed defect presents, i.e., if in a subpopulation of 500 women the same rare adverse effect is observed this is a pretty compelling argument that the drug may present a hazard. Pregnancy registry data are being interpreted by a group of experts.

Pregnancy registries should be considered when animal findings are of concern or ambiguous (which is not to say that in the absence of such findings, pregnancy registries should not be performed), if similarity to a product exists that is known to be a concern, if human findings are of concern, if there is an expectation that there is high demand of the product in women of reproductive age, if the product is necessary to treat a condition with high morbidity during pregnancy or if live attenuated vaccines (or other products causing subclinical infections) are being used.

Pregnancy registries are considered as Phase IV commitments at the time when the product is marketed. Pregnancy registry data should be included in different part of the package insert, i.e., sections on pregnancy labeling, dosage, safety etc.

Dr. Jolson discussed two examples in which pregnancy registries were performed as Phase IV commitments:

a. The first product is Ribavirin that is given in combination with alpha interferon to treat Hepatitis C. Ribavirin has caused multiple fetal abnormalities in pre-clinical studies in all species tested. Ribavirin is given over a 6 months time period, has a long half time and is likely a human teratogen. The label contained exclusive warnings and the pregnancy category is termed "X". (It was pointed out that Schering-Plough agreed to category "X" in the label based on pregnancy studies)

b) The second drug is Efavirenz that is indicated for subjects with HIV infection. Preclinical studies revealed CNS abnormalities in 3/20 primates and the drug was considered Category C in the pregnancy label section. Efavirenz is not considered first choice of HIV drugs to be used in pregnancy.

It was stressed that the concept of performing pregnancy registries is new and that only few sponsors have conducted pregnancy registries (Merck/Varivax) In addition, it remains to be determined if data obtained from these studies can be interpreted to judge the effect of a drug on pregnancy outcome.

Dr. Jolson reviewed efforts of the clinical working group to increase reviewer and industry awareness, such as guidance documents, the reviewer training course, discussion of the topic at outside symposia and lastly the ongoing activities to re-design pregnancy section of label. The general context and goals of the reviewer guidance document "Review of Human pregnancy outcome data", the guidance for industry document "Design and Conduct of pregnancy registries", and the reviewer Training were briefly summarized (see attached slides). Concern was expressed that any one committee may not be able to address all of industry and the suggestion was made to have a FDA workshop on the concept of pregnancy registries. It was mentioned that the DIA meeting would also have discussions on pregnancy registries.

Dr. Jolson concluded her presentation with the remark that one key to improve the pregnancy label lies in the availability of human data and in FDA's ability to interpret these data soundly. Data obtained from pregnancy registries should help to meet this goal whereby the philosophy is "Some information is better than no information". Pregnancy registries may provide reasonable information about human pregnancy outcome data in the absence of controlled clinical trials.

Suggestions were made to contact staff at the National Institutes of Child Health (NICHD), D. Alexander, for participation in the work of the pregnancy registry working group. Dr. Jolson asked that suggestions should be mailed to her E-mail account. Dr. Jolson announced that the next scheduled meeting of the pregnancy registry working group is November 17, 1998.

The group discussed the need to obtain data on human pregnancy outcome on currently licensed vaccines recommended for pregnant women. For example, the label for the influenza vaccine states Category C. No animal data exist. It is at the physicians discretion to assess the risk benefit. However, the ACIP recommended that this vaccine can be given to pregnant women in their second trimester. This recommendation was included in the package insert. The question was raised why such recommendations was put in the label in the absence of data.

2. Status update point paper "Preclinical reproductive toxicity study requirements for vaccines"

M. Gruber informed the group that the point paper "Reproductive toxicity study requirements for vaccines" was presented at CBER staff meeting on September 23, 1998. The paper was subsequently distributed to all division directors within OVRR. The comment period will end on November 15, 1998. So far, no comments were received. Once the comment period has passed, the paper will be presented to Dr. Devine. A copy of the paper was also provided to Dr. Zoon. The purpose of the point paper is to obtain feedback from CBER management on the recommendations made by the maternal immunization working group, to obtain concurrence that these recommendations be used in discussing reproductive toxicity study requirements with sponsors and to generate a working document to promote consistency among OVRR reviewers. At this time the paper is not viewed as a guidance document for preclinical repro-tox testing for vaccines. The development of such document may be a next step following concurrence from CBER management on the recommendations contained in the point paper.

3. Thimerosal as a preservative in vaccine products

There was further discussion with regard to the presence of thimerosal in vaccine products. Dr. Hastings informed the group that a Pharm/Tox reviewer (Steve Hundley) at DSPIDP has conducted a review of the published pharmacology and toxicology information on thimerosal. The conclusion was that there is little information in the available literature to support the view of thimerosal being a significant hazard at the doses used in vaccine products. However, it appears that reproductive toxicity studies and pharmaco-kinetic studies to evaluate the metabolism of thimerosal have not been conducted. Thus, there is no scientific data base from which to derive regulatory recommendations. It was discussed that toxicity studies with thimerosal may be conducted at FDA's contract laboratories, other Institutions such as the National Center for Toxicology Research (NCTR) were also mentioned. Dr. Hastings indicated that such a study could perhaps be conducted at CDER Office of Testing and Research (OTR)under the direction of Frank Sistare (see also

E-Mail from Dr. Hastings to Dr. Hardegree attached). Such study could potentially be set up as a CRADA with participation of various companies.

Attachments:

1. Overheads "Pregnancy registries initiative"
2. Point paper: "Preclinical reproductive toxicity study requirements for vaccines"
3. E-Mail from Dr. Hastings to Dr. Hardegree (10/14/98) "Thimerosal"
4. Attendees list

Brockner Ryan, Beth

om: Patriarca, Peter
nt: Friday, July 02, 1999 10:24 AM
To: BACHORIK, LAWRENCE
Cc: Baylor, Norman; Esber, Elaine; Goldenthal, Karen; Ball, Leslie; Deal, Carolyn D.
Subject: RE: Q and As

Sensitivity: Confidential

Larry: I also have a few suggestions and some "heads-up's" which you may wish to consider ... they represent my own personal views, and, in the interest of time, have not been cleared by my superiors.

You may wish to point out that (1) FDA continuously examines safety, potency, and purity issues for all vaccines and works closely with manufacturers to improve every product wherever and whenever possible [i.e., the thimerosal issue is part of larger, global effort to make vaccines even more safe and efficacious than they currently are]; (2) FDA began the process of encouraging thimerosal-free preparations before FDAMA through the IND and pre-PLA processes [I'm not sure if we can compile specific examples rapidly ... Karen Goldenthal may know]; and (3) thimerosal has potential benefits as well as potential risks -- it's not simply a matter of "thimerosal is a totally inert, unnecessary ingredient, and is potentially bad ... so let's get rid of it". Thimerosal has been an important component in the manufacturing of certain vaccines, and the addition of thimerosal to the final (multi-dose) container provides additional assurances that the product will not become contaminated with bacteria once the vial is entered by the practitioner. In addition, removal of thimerosal -- if and whenever possible [and FDA is now actively pursuing this, as you probably know] -- could have other important "non-medical" downsides, including the potential elimination of multi-dose presentations for certain vaccines, which will (i) increased the cost of vaccines; and (ii) increase storage [space] requirements in the clinic setting. You should also be aware that if the U.S. (and perhaps the EU) adopts a position that the theoretical risk of ethyl mercury exposure outweigh its potential benefits to the point where no vaccines used in the US or Europe will contain thimerosal [which is where things appear to be headed], this could also have a severe impact on global ("third world") vaccination programs, particularly for hepatitis B and whole-cell DTP vaccines, which, for various reasons, will almost certainly have to have thimerosal as an ingredient for potentially many years to come. WHO has already made a plea to the Academy of Pediatrics to "tread lightly" and "consider the global ramifications" of their evolving policy.

Finally, in my own personal opinion -- and as a heads-up because I believe it could come up -- the greatest point of vulnerability on this issue is that the systematic review of thimerosal in vaccines by the FDA could have been done years and on an ongoing basis as the childhood immunization schedule became more complex. The calculations done by A are not complex. I'm not sure if there will be an easy way out of the potential perception that the FDA, CDC and immunization policy bodies may have been "asleep at the switch" re: thimerosal until now.

-----Original Message-----
From: Ball, Leslie
Sent: Thursday, July 01, 1999 11:08 PM
To: BACHORIK, LAWRENCE
Cc: Baylor, Norman; Esber, Elaine; Patriarca, Peter; Goldenthal, Karen
Subject: Q and As
Sensitivity: Confidential

Larry:

Attached are my suggested revisions to the Q and As. Regarding the literature review, we found several reports of acute toxicity at high doses, as well as hypersensitivity reactions at low doses, especially from topical exposure. Regarding the VAERS search, there were 45 reports in the VAERS database from 1990 to 1998 for thimerosal. Most reports involved allergic reactions (hypersensitivity), although a cause-and-effect relationship could not be established.

I hope this helps.

<< File: thimerosalQA1.doc >>

PENGAD-Bayonne, N.J.
EXHIBIT
16

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A POPULATION-BASED STUDY OF MEASLES, MUMPS, AND RUBELLA VACCINATION AND AUTISM

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ABSTRACT

Background It has been suggested that vaccination against measles, mumps, and rubella (MMR) is a cause of autism.

Methods We conducted a retrospective cohort study of all children born in Denmark from January 1991 through December 1998. The cohort was selected on the basis of data from the Danish Civil Registration System, which assigns a unique identification number to every live-born infant and new resident in Denmark. MMR-vaccination status was obtained from the Danish National Board of Health. Information on the children's autism status was obtained from the Danish Psychiatric Central Register, which contains information on all diagnoses received by patients in psychiatric hospitals and outpatient clinics in Denmark. We obtained information on potential confounders from the Danish Medical Birth Registry, the National Hospital Registry, and Statistics Denmark.

Results Of the 537,303 children in the cohort (representing 2,129,864 person-years), 440,655 (82.0 percent) had received the MMR vaccine. We identified 316 children with a diagnosis of autistic disorder and 422 with a diagnosis of other autistic-spectrum disorders. After adjustment for potential confounders, the relative risk of autistic disorder in the group of vaccinated children, as compared with the unvaccinated group, was 0.92 (95 percent confidence interval, 0.68 to 1.24), and the relative risk of another autistic-spectrum disorder was 0.83 (95 percent confidence interval, 0.65 to 1.07). There was no association between the age at the time of vaccination, the time since vaccination, or the date of vaccination and the development of autistic disorder.

Conclusions This study provides strong evidence against the hypothesis that MMR vaccination causes autism. (N Engl J Med 2002;347:1477-82.)

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IT has been suggested that the measles, mumps, and rubella (MMR) vaccine causes autism.[1-4] The widespread use of the MMR vaccine has reportedly coincided with an increase in the incidence of autism in California,[5] and there are case reports of children in whom signs of both developmental regression and gastrointestinal symptoms developed shortly after MMR vaccination.[1] Measles virus has been found in the terminal ileum in children with developmental disorders and gastrointestinal symptoms but not in developmentally normal children with gastrointestinal symptoms.[6] The measles virus used in the MMR vaccine is a live attenuated virus that normally causes no symptoms or only very mild ones. However, wild-type measles can infect the central nervous system and even cause postinfectious encephalomyelitis, probably as a result of an immune-mediated response to myelin proteins.[7-9]

Studies designed to evaluate the suggested link between MMR vaccination and autism do not support an association, but the evidence is weak and based on case-series, cross-sectional, and ecologic studies. No studies have had sufficient statistical power to detect an association, and none had a population-based cohort design.[10-16] The World Health Organization and other organizations have requested further investigation of the hypothetical association between the MMR vaccine and autism.[2,17-20] We evaluated the hypothesis in a cohort study that included all children born in Denmark in 1991 through 1998.

From the Danish Epidemiology Science Center, Department of Epidemiology and Social Medicine, Århus, Denmark (K.M.M., M.V., P.T., J.O.); the Danish Epidemiology Science Center, Department of Epidemiology Research, Statens Serum Institute, Copenhagen, Denmark (A.H., J.W., M.M.); and the National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta (D.S.). Address reprint requests to Dr. Madsen at the Danish Epidemiology Science Center, Department of Epidemiology and Social Medicine, Vennelyst Blvd. 6, DK-8000, Aarhus C, Denmark, or at kmm@dadlnet.dk.

EXHIBIT
17

METHODS

Study Design

We designed a retrospective follow-up study of all children born in Denmark during the period from January 1, 1991, to December 31, 1998. The cohort was established on the basis of data obtained from the Danish Civil Registration System and five other national registries.

All live-born children and new residents in Denmark are assigned a unique personal identification number (a civil-registry number), which is stored in the Danish Civil Registration System together with information on vital status, emigration, disappearance, address, and family members (mother, father, and siblings).[21] The registry is updated once a week, and all changes in the stored information are reported to the registry according to established legal procedures. The civil-registry number is used as the link to information at the individual level in all other national registries. This system provides completely accurate linkage of information between registries at the individual level.

We determined MMR-vaccination status on the basis of vaccination data reported to the National Board of Health by general practitioners, who administer all MMR vaccinations in Denmark. The general practitioners are reimbursed by the state on the basis of these reports. We retrieved information on vaccinations from 1991 through 1999. The MMR vaccine was introduced in Denmark in 1987, and the single-antigen measles vaccine has not been used. The MMR vaccine used in Denmark during the study period was identical to that used in the United States and contained the following vaccine strains: Moraten (measles), Jeryl Lynn (mumps), and Wistar RA 27/3 (rubella).

The national vaccination program recommends that children be vaccinated at 15 months of age and again at 12 years. No change was made in the program during the study period. We obtained information on MMR vaccination at 15 months of age, since only this exposure is relevant to the end point under study. Since the vaccination data are transferred to the National Board of Health once a week, we chose Wednesday as the day of vaccination. When the vaccination information was recorded with the child's own civil-registry number, the information was directly linked with other registries. Before 1996, in most cases the vaccination information and the age of the child were recorded with the civil-registry number of the accompanying adult; we used information from the Danish Civil Registration System to identify the link from the accompanying adult to the child. Thus, 98.5 percent of the children were identified with the use of the child's civil-registry number or the civil-registry number of the mother or father and the age of the child at vaccination. The remaining 1.5 percent of children were identified on the basis of additional information from the Danish Civil Registration System on other relatives and information on the address at the time of vaccination.

Information about diagnoses of autism was obtained from the Danish Psychiatric Central Register, which contains information on all diagnoses received by patients in psychiatric hospitals, psychiatric departments, and outpatient clinics in Denmark.[22] In our cohort, 93.1 percent of the children were treated only as outpatients, and 6.9 percent were at some point treated as inpatients in a psychiatric department. All diagnoses were based on the *International Classification of Diseases, 10th Revision* (ICD-10), which is similar to the 4th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) with regard to autism.[23-26] In Denmark, children are referred to specialists in child psychiatry by general practitioners, schools, and psychologists if autism is suspected. Only specialists in child psychiatry diagnose autism and assign a diagnostic code, and all diagnoses are recorded in the Danish Psychiatric Central Register. We identified all children given a diagnosis of autistic disorder (ICD-10 code F84.0 and DSM-IV code 299.00) or another autistic-spectrum disorder (ICD-10 codes F84.1 through F84.9 and DSM-IV codes 299.10 and 299.80). When a child was given diagnoses of both autistic disorder and one or more other autistic-spectrum disorders, we classified the diagnosis as autistic disorder. Autism is associated with the inherited genetic conditions tuberous sclerosis, Angelman's syndrome, and the fragile X syndrome and with congenital rubella. To maximize the homogeneity of the study population, data for children with these conditions were censored when the diagnosis was made. We obtained information on these conditions from the National Hospital Registry.

We performed an extensive record review for 40 children with autistic disorder (13 percent of all the children with autistic disorder) to validate the diagnosis of autism. A consultant in child psychiatry with expertise in autism examined the medical records. Thirty-seven of the children (92 percent) met the operational criteria for autistic disorder according to a systematic coding scheme developed by the Centers for Disease Control and Prevention for surveillance of autism and used in a prevalence study in Brick Township, New Jersey.[27] The three children who did not meet the criteria for autistic disorder were all classified as having other autistic-spectrum disorders. For two of the children, the diagnosis of autistic disorder was questionable because of profound intellectual impairment. For the third child, we did not have information about the onset of symptoms before the age of three years, which is a prerequisite for the diagnosis of autistic disorder.

We obtained information on birth weight and gestational age from the Danish Medical Birth Registry and the National Hospital Registry.[28,29] Information on potential confounders, including socioeconomic status (as indicated by the employment status of the head of the household) and mother's education was obtained from Statistics Denmark from the time when the child was 15 months of age.

Statistical Analysis

Follow-up for the diagnosis of autistic disorder or another autistic-spectrum disorder began for all children on the day they reached one year of age and continued until the diagnosis of autism or an associated condition (the fragile X syndrome, Angelman's syndrome, tuberous sclerosis, or congenital rubella), emigration, death, or the end of follow-up, on December 31, 1999, whichever occurred first. The incidence-rate ratios for autistic disorder and other autistic-spectrum disorders in the group of vaccinated children, as compared with the unvaccinated group, were examined in a log-linear Poisson regression model with the use of PROC GENMOD (SAS, version 6.12).[30] We treated vaccination as a time-dependent covariate. The children were assigned to the nonvaccinated group until they received the MMR vaccine. From that date, they were followed in the vaccinated group. In additional analyses, the MMR-vaccinated children were grouped according to their age at the time of vaccination, the interval since vaccination, and the calendar period when vaccination was performed.

In reporting the results, we refer to the incidence-rate ratios as relative risks. For all risk estimates, we considered possible confounding by age (1, 2, 3, 4, 5, 6, 7, or 8 to 9 years), sex, calendar period (1992 to 1993, 1994, 1995, 1996, 1997, 1998, or 1999; for other autistic-spectrum disorders, the years 1992, 1993, and 1994 were grouped together), socioeconomic status (six groups), mother's education (five groups), gestational age (≤36, 37 to 41, or ≥42 weeks), and birth weight (≤2499, 2500 to 2999, 3000 to 3499, 3500 to 3999, or ≥4000 g).

RESULTS

A total of 537,303 children were included in the cohort and followed for a total of 2,129,864 person-years. Follow-up of 5811 children was stopped before December 31, 1999, because of a diagnosis of autistic disorder (in 316 children), other autistic-spectrum disorders (in 422), tuberous sclerosis (in 35), congenital rubella (in 2), or the fragile X or Angelman's syndrome (in 8), and because of death or emigration in the cases of 5028 children, whose data were censored. For children who received MMR vaccine, there were 1,647,504 person-years of follow-up, and for children who did not receive the vaccine, there were 482,360 person-years of follow-up.

Table 1 shows the distribution of the MMR cohort according to vaccination status, sex, birth weight, gestational age, socioeconomic status, mother's education, and age when autism was diagnosed. The mean age at diagnosis was four years and three months for autistic disorder and five years and three months for other autistic-spectrum disorders. The mean age at the time of the MMR vaccination was 17 months, and 98.5 percent of the vaccinated children were vaccinated before 3 years of age. The proportion of children who were vaccinated was the same among boys and girls (82.0 percent).

Table 2 shows the association between variables related to MMR vaccination and the risk of autism. We calculated the relative risk with adjustment for age, calendar period, sex, birth weight, gestational age, mother's education, and socioeconomic status. Overall, there was no increase in the risk of autistic disorder or other autistic-spectrum disorders among vaccinated

TABLE 1. CHARACTERISTICS OF THE 537,303 CHILDREN IN THE DANISH COHORT.

CHARACTERISTIC	VACCINATED CHILDREN (N=440,655)	UNVACCINATED CHILDREN (N=96,648)	P VALUE*
	number (percent)		
Sex			0.55
Male	226,042 (51.3)	49,680 (51.4)	
Female	214,613 (48.7)	46,968 (48.6)	
Birth weight			<0.001
≤2499 g	21,633 (4.9)	5,164 (5.3)	
2500–2999 g	53,874 (12.2)	12,062 (12.5)	
3000–3499 g	135,630 (30.8)	29,262 (30.3)	
3500–3999 g	135,255 (30.7)	29,143 (30.2)	
≥4000 g	66,358 (15.1)	14,563 (15.1)	
Data missing	27,905 (6.3)	6,454 (6.7)	
Gestational age			<0.001
≤36 wk	19,029 (4.3)	3,129 (3.2)	
37–41 wk	272,345 (61.8)	40,609 (42.0)	
≥42 wk	27,349 (6.2)	3,986 (4.1)	
Data missing†	121,932 (27.7)	48,924 (50.6)	
Socioeconomic status‡			<0.001
Manager (very high)	41,367 (9.4)	9,940 (10.3)	
Wage earner (high)	85,772 (19.5)	16,187 (16.7)	
Wage earner (medium)	70,906 (16.1)	13,753 (14.2)	
Wage earner (low)	116,503 (26.4)	26,699 (27.6)	
Wage earner (minimal)	57,408 (13.0)	10,996 (11.4)	
Unemployed	67,841 (15.4)	18,519 (19.2)	
Data missing	858 (0.2)	554 (0.6)	
Mother's education			<0.001
Postgraduate education	26,118 (5.9)	5,856 (6.1)	
College	67,776 (15.4)	14,599 (15.1)	
Vocational training	178,553 (40.5)	34,006 (35.2)	
Secondary school	42,667 (9.7)	10,164 (10.5)	
Primary school	114,768 (26.0)	28,680 (29.7)	
Data missing	10,773 (2.4)	3,343 (3.5)	
Age at diagnosis of autistic disorder			0.87
≤2 yr	48 (0.01)	9 (0.01)	
3–5 yr	187 (0.04)	31 (0.03)	
≥6 yr	34 (0.01)	7 (0.01)	
Age at diagnosis of another autistic-spectrum disorder			0.19
≤2 yr	32 (0.01)	3 (0.003)	
3–5 yr	202 (0.05)	37 (0.04)	
≥6 yr	118 (0.03)	30 (0.03)	

*P values are based on the chi-square test of statistical independence.

†Data were available from the Danish Medical Birth Registry only until December 31, 1996.

‡The employment status of the head of the household was used to indicate socioeconomic status.

Table 2. Adjusted Relative Risk of Autistic Disorder and of Other Autistic-Spectrum Disorders in Vaccinated and Unvaccinated Children.*

Vaccination	Person-Years†	Autistic Disorder		Other Autistic Spectrum Disorders	
		No. of cases	Adjusted relative risk (95% CI)	No. of cases	Adjusted relative risk (95% CI)
Total	2,129,864	316		422	
Vaccination					
No	482,360	53	1.00	77	1.00
Yes	1,647,504	263	0.92 (0.68–1.24)	345	0.83 (0.65–1.07)
Age at vaccination					
Not vaccinated	482,360	53	1.00	77	1.00
≤14 mo	200,003	38	1.18 (0.78–1.80)	43	0.88 (0.60–1.28)
15–19 mo	1,320,753	195	0.86 (0.63–1.17)	270	0.83 (0.64–1.08)
20–24 mo	69,242	17	1.19 (0.69–2.07)	12	0.62 (0.33–1.13)
25–35 mo	40,935	11	1.20 (0.63–2.31)	15	1.09 (0.63–1.91)
≥36 mo	16,572	2	0.56 (0.14–2.30)	5	0.64 (0.26–1.59)
Interval since vaccination					
Not vaccinated	482,360	53	1.00	77	1.00
<6 mo	212,805	3	0.39 (0.11–1.32)	8	1.18 (0.51–2.75)
6–11 mo	197,931	21	1.38 (0.76–2.51)	4	0.31 (0.10–0.91)
12–17 mo	183,460	22	1.07 (0.59–1.95)	16	0.92 (0.47–1.80)
18–23 mo	168,045	31	0.86 (0.52–1.41)	16	0.47 (0.26–0.86)
24–29 mo	154,290	42	0.99 (0.61–1.58)	32	0.77 (0.46–1.27)
30–35 mo	139,258	33	0.86 (0.54–1.38)	27	0.69 (0.43–1.11)
36–59 mo	406,320	90	0.99 (0.66–1.50)	158	1.05 (0.77–1.45)
≥60 mo	185,396	21	0.67 (0.34–1.33)	84	0.75 (0.51–1.09)
Date of vaccination					
Not vaccinated	482,360	53	1.00	77	1.00
1991–1992	248,646	31	1.00 (0.59–1.70)	61	0.75 (0.51–1.09)
1993–1994	659,152	81	0.73 (0.50–1.06)	146	0.74 (0.56–0.99)
1995–1996	475,990	96	0.91 (0.63–1.30)	116	1.13 (0.81–1.56)
1997–1999	263,716	55	1.35 (0.84–2.17)	22	0.71 (0.40–1.24)

*The relative risk was adjusted for age, calendar period, sex, birth weight, gestational age, mother's education, and socioeconomic status of the family. The reference group was the group of children who were not vaccinated. The distribution of cases of autistic disorder or other autistic-spectrum disorders according to vaccination status differs from that in Table 1 because, in this analysis, children who were vaccinated after the disorder had been diagnosed were classified according to their vaccination status at the time of the diagnosis (i.e., as unvaccinated). CI denotes confidence interval.

†Because of rounding, the numbers of person-years do not necessarily sum to the total shown.

children as compared with unvaccinated children (adjusted relative risk of autistic disorder, 0.92; 95 percent confidence interval, 0.68 to 1.24; adjusted relative risk of other autistic-spectrum disorders, 0.83; 95 percent confidence interval, 0.65 to 1.07). Furthermore, we found no association between the development of autistic disorder and the age at vaccination (P=0.23), the interval since vaccination (P=0.42), or the calendar period at the time of vaccination (P=0.06).

Adjustment for potential confounders with the exception of age resulted in similar estimates of risk. Changing the start of follow-up for autistic disorder and other autistic-spectrum disorders to the date of birth or 16 months of age had little effect on the estimates (data not shown). Furthermore, including children with the fragile X syndrome, tuberous sclerosis, congenital rubella, or Angelman's syndrome in the analysis did not change the estimates (data not shown).

DISCUSSION

This study provides three strong arguments against a causal relation between MMR vaccination and autism. First, the risk of autism was similar in vaccinated and unvaccinated children, in both age-adjusted and fully adjusted analyses. Second, there was no temporal clustering of cases of autism at any time after immunization. Third, neither autistic disorder nor other autistic-spectrum disorders were associated with MMR vaccination. Furthermore, the results were derived from a nationwide cohort study with nearly complete follow-up data.

All previous studies of an association between autism and MMR vaccination have been case series,[1,14,15] ecologic studies,[11,12] or cross-sectional studies,[10,13] and the majority have not used optimal data for risk assessment. In a well-conducted, cross-sectional prevalence study, Taylor and colleagues[10] found that there was no sharp increase in the prevalence of autism after the introduction of the MMR vaccine. However, it could be argued that a more gradual increase would be expected, since autism is characterized by an insidious onset and a delay in diagnosis. A case-series study by Peltola et al.[15] also provides evidence against a causal connection.

One of the main reasons for public concern has been that the widespread use of the MMR vaccine in some regions appeared to coincide with an increase in the incidence of autism. However, this is not a uniform finding. In Denmark, the prevalence of autism (according to the criteria of the *International Classification of Diseases, 8th Revision*) was less than 2.0 cases per 10,000 children between the ages of five and nine years in the 1980s and the beginning of the 1990s. Since then, the rates have increased in all age groups except for children younger than two years of age, and in 2000, the prevalence of autism (according to the ICD-10 criteria) was higher than 10.0 cases per 10,000 children five to nine years of age (unpublished data). Thus, the increase in autism both in California[5] and in Denmark occurred well after the introduction of the MMR vaccine.

Our study was based on individual reports of vaccination and diagnoses of autism in a well-defined geographic area. The exposure data were collected prospectively, independently of parental recall and before the diagnosis of autism. Furthermore, the diagnosis was recorded independently of the recording of MMR vaccination. Thus, there was little possibility of differential misclassification of exposure or outcome measures. Furthermore, our analysis was based on complete follow-up data.

We assume that the data on MMR vaccination are almost complete, since general practitioners in Denmark are reimbursed only after reporting immunization data to the National Board of Health. We had an unvaccinated reference group with almost 500,000 person-years of follow-up, even though the study was numerically imbalanced in favor of the vaccinated group. The power of the study is reflected in the narrow 95 percent confidence intervals.

We had no information on the presence or absence of a family history of autism, which could explain our negative findings only if families with a history of autism avoided MMR vaccination. If so, we would expect to have found high relative risks at the beginning of the study period, before the hypothetical link between vaccination and autism was publicized. This was not the case. We had no information on whether the children with autism had regression, and thus we could not perform a subgroup analysis. However, the fact that the overall relative risk of autism or an autistic-spectrum disorder was less than 1.0 does not support the possibility of a subgroup of vulnerable children.

The Danish vaccination program recommends that children receive the MMR vaccine at 15 months of age and provides the vaccination free of charge. Among the children in our cohort who were born in 1995, the rate of MMR vaccination was lower than the rate of vaccination with the first *Haemophilus influenzae* type B vaccine (86.9 percent vs. 97.0 percent). However, the rate of MMR vaccination in our study was similar to that in the United States (87.6 percent in 1995) and Belgium (83.0 percent in 1997).[31,32] Nevertheless, the main concern is the comparability of vaccinated and nonvaccinated children in relation to the end point under study. In all analyses, when risk estimates were calculated, we controlled for possible confounders (age, sex, calendar period, socioeconomic status, mother's education, gestational age, and birth weight). Except for age, none of these possible confounders changed the estimates. The confounding by age was a function of the time available for follow-up, since much of the follow-up for the unvaccinated group involved young children, in whom autism is often undiagnosed.

We assessed the validity of the diagnosis of autistic disorder in a subgroup of children and found it to be high. This was to be expected, since only specialists in child and adolescent psychiatry are authorized to code the diagnosis of autism in the Danish Psychiatric Central Register. All schools have access to health care personnel as well as psychologists. Because of the comprehensive health care surveillance for children in Denmark, all severe cases of autism are likely to be diagnosed and reported to the registry at some point. Reporting of the other autistic-spectrum disorders is less complete than that for autistic disorder, and some diagnoses are almost certainly missed. However, it is unlikely that this misclassification would be associated with vaccination status. It is very difficult to determine the onset of autism, and many cases are probably due to prenatal factors. Our records did not contain information on when the first autistic symptoms were noted, and we could not adjust for a differential delay in the diagnosis. Again, it is highly unlikely that a delayed diagnosis was associated with MMR vaccination in this study.

There are few published data on the incidence of autism, but the prevalence rates reported in the literature vary widely, from 1.2 cases per 10,000 (according to the criteria of the third edition of the *Diagnostic and Statistical Manual of Mental Disorders*) to 30.8 per 10,000 (according to the ICD-10 criteria).[33,34] The prevalence rates among eight-year-old children in our cohort were 7.7 per 10,000 for autistic disorder and 22.2 per 10,000 for other autistic-spectrum disorders. These rates are similar to the prevalence rates of 5.4 per 10,000 for autistic disorder and 16.3 per 10,000 for other autistic-spectrum disorders in a cohort of 325,347 French children (ICD-10 criteria), reported by Fombonne et al.,[35] and the rate of 11 per 10,000 for autistic disorder in a cohort of U.S. children (DSM-IV criteria), reported by Croen and colleagues.[36] The DSM-IV classification system used in the United States and the ICD-10 classification system used in many European countries are almost identical with regard to the classification of autistic disorder.[23-26] In our validity substudy, we found that 93 percent of cases diagnosed according to the ICD-10 criteria met the DSM-IV operational criteria for the diagnosis of autistic disorder.

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August 27, 2001

Chairman Dan Burton
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Dear Mr. Chairman:

The National Institutes of Health (NIH) welcomes the opportunity to further explore topics regarding autism and mercury exposure raised at the recent hearing entitled "Autism – Why the Increased Rates? A One Year Update." The following responses are provided to the follow-up questions from the hearing.

1. In the University of Rochester study which measured mercury levels in infants after vaccines, what were the levels of exposures? Previous exposures resulted in 62.5 mcg ethyl-mercury exposure at two months of age and cumulative exposure of 187.5 mcg. How long after the administration of the vaccines were the blood samples collected? How do you explain that the levels found in this study directly conflict with those of Stajitch, who found mercury levels in pre-term infants ten-fold higher after exposure, and one infant in the study developed a mercury level of 23.6 mcg. We know that levels between 15 and 30 mcg may result in neuro-developmental abnormality-as was the case with acrodynia. Of thousands of infants exposed to mercury in teething powder, only one in 500 developed acrodynia. Is it not true that this study, with only 60 infants studied, is too small to identify sensitive infants? Your testimony mentions that the Rochester study took samples of mercury in the serum, hair and urine but only references the result of analyzing the blood. As we learned from expert testimony during the hearing, analyzing the hair and urine is crucial. Why was this not done? Please provide the committee the complete analysis.

   Response – Dr. John Treanor conducted the University of Rochester study, "Evaluation of Mercury in Infants After Receipt of Vaccines Containing Thimerosal." This study, supported by the National Institute of Allergy and Infectious Diseases, was to determine levels of mercury in blood in infants following routine vaccination according to the U.S. immunization schedule. The subjects included two groups: two month-old infants and six month-old infants. The mean mercury exposure in the two month-old group was 45.6 micrograms and the mean mercury exposure in the six month-old group was 111.3 micrograms. All samples were collected between three and 30 days of vaccination, with the majority being collected within two weeks of vaccination.

   It is difficult to compare the Stajitch study, where all samples were taken two to three days after vaccination, with the Rochester study, where samples were collected over a longer period of time during which mercury was being metabolized and eliminated. However, in examining the data from the two studies it is interesting to note that the Rochester data and the Stajitch data for term infants are actually quite comparable. The

EXHIBIT
18

Rochester study reported a mean blood mercury level for the two month-old cohort of 1.50 micrograms per liter (range less than 0.75 – 4.11) compared to the Stajitch study, which reported a mean blood mercury level for newborns of 2.24 micrograms per liter (range 1.4-2.9). The pre-term group of the Stajitch study had mean blood mercury levels of 7.36 micrograms per liter (range 1.3-23.6). As suggested in the Stajitch paper, the higher concentrations of mercury found in the pre-term group could be attributed to their decreased ability to metabolize and eliminate mercury and the smaller volume of distribution (size).

The objective of the Rochester study was to measure levels of mercury in blood in infants following routine vaccination according to the U.S. immunization schedule. The study was not designed to identify the effects of mercury exposure. In addition to an analysis of whole blood, urine and stool samples within 30 days of vaccination, some vaccine, formula, breast milk and maternal hair samples also were tested. While analysis of blood samples has been completed, work is continuing on the analysis of the urine and stool samples. We will be pleased to provide you with the study results once they have been released.

2. How will large prospective studies looking at the potential vaccine link to autism factor in the transition to thimerosal-free vaccines? Isn't it true, that while valuable, these studies will not be able to give us answers about mercury toxicity through vaccinations?

Response – Large, prospective longitudinal studies, such as the National Longitudinal Cohort Study of Environmental Effects on Child Health and Development, where 100,000 infants or more are followed from pregnancy through adulthood, will enable the identification of children who show particular sensitivity or susceptibility to different environmental exposures. Because the National Longitudinal Cohort Study of Environmental Effects on Child Health and Development will not be enrolling participants until several years from now, the vaccines they receive will not contain thimerosal. Thus, although such studies will be able to assess exposures to other sources of mercury (air pollution, diet, etc.) they will not be able to give answers regarding the past effect of thimerosal in concentrations needed to function as a preservative in vaccines.

Epidemiological studies, especially those using existing patient data bases, such as the Centers for Disease Control and Prevention (CDC) Metropolitan Atlanta study data, will have an opportunity to monitor the relationship between vaccines with and without thimerosal as a preservative and the incidence of autism. In addition, the patients in the Collaborative Programs of Excellence in Autism (CPEA) Network Autism Regression/Vaccine Study will have received the thimerosal-containing vaccines. In this study, an analysis of the temporal relationship between administration of vaccines and parental report of onset of symptoms both in children with autism and healthy controls should shed some light on the matter of thimerosal and onset of autism, though lab tests are not expected to be able to detect thimerosal so long after vaccination in the children who are being evaluated as part of this study.

3. On page 9 of your testimony, you mentioned the CPEA initiative on Autism Regression/Vaccination Study. Please describe this in greater detail? Are you specifically looking at tissue samples from these children? Are you using the same precise detection devices that Dr. Wakefield used to determine if there is vaccine-strain measles virus present? When do you expect to have this study completed?

Response – As indicated in the NIH testimony at the hearing before your Committee on April 26, 2001, the National Institute of Child Health and Human Development (NICHD), National Institute on Deafness and Other Communication Disorders (NIDCD), and CDC are supporting the ongoing CPEA Autism Regression/Vaccine Study. The principal goal of this study is to assess the temporal association between the administration of measles/mumps/rubella (MMR) vaccine and onset of autism, differentiating early- and late-onset forms of the disorder. An additional goal of the study is to try to replicate the findings of studies that have reported persistent measles infection in autism cases versus healthy controls.

Stage 1 of the study, which began in September 2000, will examine the medical and developmental records of 1,600 well-diagnosed cases of autism, as well as those of 1,250 healthy controls to assess the temporal relationship between receipt of vaccines, especially MMR vaccine, and the onset of symptoms in early onset autism, regressive autism, and healthy controls. Stage 2 of the study will use laboratory tests to assess the levels of measles antibody titers and to search for evidence of persistent measles infection in blood that could be attributed to the MMR vaccine in 250 early onset autism cases and 250 matched controls, and 250 regressive autism cases (children who regress to autism after apparently healthy early development) and 250 matched controls. Procedures to be used in Stage 2 of the study include standard serology tests such as those used by Dr. Singh, and Real Time PCR tests used by Dr. Wakefield's group. To the extent that we are able to get full details of Dr. Wakefield and Dr. O'Leary's procedures, the CPEA Network study tests will replicate and extend the methodology used by them to test the hypotheses they raised. Entercolitis tissue samples will be collected and analyzed only if the results of Stage 1 and Stage 2 studies indicate that such invasive procedures are warranted. We anticipate that Stage 1 of the study will be completed in Fiscal Year 2002, and Stage 2 will be finished in Fiscal Year 2003.

4. On page 4 of your testimony, you stated that NIH is setting aside $1 million to fund innovative treatment proposals. You have 30 applications. How many of these proposals do you think you will be able to fund with $1 million? Don't you think that a larger commitment is needed to address the needs of an epidemic?

Response – The National Institute of Mental Health (NIMH), acting for the participating NIH institutes (NIMH, NICHD, NINDS, and NIDCD), received 30 applications in response to Request for Applications (RFA) MH-01-101, "Development of Innovative Treatment Approaches to Autism." A peer panel of experts will review the grants for scientific and technical merit in July 2001. We estimate that the $1 million set-aside for this RFA will enable us to fund approximately 10 innovative treatment studies. The number of applications funded will depend on the requested budgets of the fundable grants. These grants will be funded for three years for an approximate total under the RFA of $3 million. If there are highly meritorious applications that exceed the set-aside, additional funds may be utilized. Applicants whose studies are not considered by the scientific reviewers to be ready for funding will be encouraged to revise and resubmit their application at the next regular funding cycle. The NIH institutes that fund autism research maintain a commitment to funding meritorious research in treatment for autism, as stated in PA-98-108 "Research in Autism and Autism Spectrum Disorders," and qualified applications will receive priority consideration.

In addition, the five NIH Institutes pursuing autism research (NIMH, NICHD, NINDS, NIDCD, and NIEHS) have set aside a total of approximately $12 million per year to fund at least five Autism Centers, to be called STAART Centers (Studies to Advance Autism Research and Treatment). As indicated by their name, these new centers will have a major focus on the conduct of autism treatment research. Also, the CPEA Network, which is funded at over $12 million annually, will continue to address important autism treatment questions as it has in the past with studies such as the secretin trials.

5. What is the level of funding that has been expended by the NIH for extramural and intramural research to replicate Dr. Wakefield's autistic entercolitis hypothesis? If any projects have been funded, who are the principal investigators?

Response – At the present time, the CPEA Network Autism Regression/Vaccine Study is the only research underway that directly involves Dr. Wakefield's autistic entercolitis hypothesis. We anticipate that this study will expend approximately $2 million. Attached is a list of the principal investigators of the CPEA Network.

Thank you for the opportunity to testify, and continue to provide information about these important issues.

Sincerely,

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Attachment

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TOXICOLOGIC STUDIES OF SODIUM ETHYLMERCURITHIOSALICYLATE (THIMEROSAL, LILLY) IN LABORATORY ANIMALS

Compiled By

W. D. Broddle and W. R. Gibson

The Lilly Toxicology Laboratories
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February, 1973

EXHIBIT
19

Thimerosal has occupied a prominent position as a superior organomercurial antiseptic for approximately forty years. It is available in several topical forms (aerosal, cream, glycerite, ointment, solution, and tincture) in which effective concentrations are 0.1%; in an ophthalmic ointment in which the concentration is 0.02%; and has been used as a preservative in concentrations as small as 0.004%. The antimicrobial activity of thimerosal is attributed to a slow but sustained release of ethylmercuri ions from this complex organomercurial containing approximately 49% mercury.[1]

As with other chemicals of its generation, information relating to safety and efficacy of thimerosal in animal models is sparse. The following is a compilation of reports that describe the toxicity studies performed with thimerosal.

ACUTE TOXICITY

Intravenous

Mice: The first report of thimerosal toxicity to mice was that of Powell and Jamieson.[2] These investigators gave a range of intravenous doses by slow injection of 5 mg/kg to 300 mg/kg. The mice survived doses below 150 mg/kg; all doses above this quantity were lethal within 1 hour (300 mg/kg) to 3 days.

In a later study (1937) performed in the Pharmacology Division of Eli Lilly and Company,[3] fasted albino mice received intravenous doses of a 1% thimerosal preparation (vehicle unspecified). Using groups of 20 mice, doses of 30 mg/kg to 50 mg/kg were employed. From mortality data the dose calculated to be lethal to 50% of the animals (LD_{50}) was 40.9 ± 1.2 mg/kg.

A third study[3] was performed (1945) in fasted Harlan albino mice. Doses of 40-62 mg/kg of thimerosal (as the 0.1% aqueous solution) were given intravenously to groups of 10 animals. Most deaths occurred 3 days later, but a few mice died as late as 9 days post-treatment. The LD_{50} ± S.E. of this study was calculated to be 55 ± 3 mg/kg.

Rats: In an initial study[2] of thimerosal administered intravenously to rats, doses ranging between 30 and 70 mg/kg were used. A total of 62 rats was used to evaluate the toxicity of 7 different lots of thimerosal. The conclusions were that 45 mg/kg was the tolerated intravenous dose in this species.

Autopsy of some of these rats as well as other rats given subcutaneous doses revealed definite kidney lesions consisting prinicipally of tubular changes, including necrosis of the epithelium, inclusion of masses of debris in the lumen, and congested and hemorrhagic regions throughout the cortex.

Rabbits: Powell and Jamieson[2] reported having administered thimerosal intravenously to more than 300 rabbits. They indicated that injections of 1% solutions were administered slowly and that 25 mg/kg was the usual tolerated dose. Antemortem evidence of toxicity included prostration and diarrhea. Deaths occurred from 1 to 6 days post-treatment and cause of death was attributable to mercurial poisoning, including kidney and intestinal lesions.

4

Lequesne, et al.,[4] reported dosing two groups of male rabbits with thimerosal, 20 or 60 mg/kg. The compound was given intravneously in 10-20 ml normal saline over a 10-minute interval. Onset of side effects and deaths seen at both doses varied with the dose and rate of injection. Side effects noted were drowsiness, ataxia, weight loss, and oliguria. Animals receiving a dose of 60 mg/kg showed a progressive fall in serum potassium and an elevation in urinary potassium excretion. Histopathology included kidney tubular necrosis but no glomerular lesions.

4

Oral

Rats: In a series of four studies,[3] fasted female Harlan rats were treated orally with aqueous solutions of thimerosal varying in concentration from 0.5% to 2%. In these trials groups of 10 rats received oral doses of 45 to 125 mg/kg.

An oral dose of 50 mg/kg, given as thimerosal, 0.5% in aqueous solution caused no overt evidence of toxicity during a 7-day observation period. In contrast, other rats given 100 mg/kg as thimerosal, 2%, in aqueous solution died within 24 hours. The LD_0 was greater than 50 and the LD_{100} was less than 100 mg/kg.

In another study using 0.5% thimerosal in aqueous solution, a range of doses from 45 to 100 mg/kg was employed. Hypoactivit ptosis, chromorhinorrhea, poor grooming, and weakness preceded deaths, which occurred from 2 to 6 days post-treatment. The LD_{50} ± S.E. after 7 days was 96.9 ± 8.3 mg/kg.

Because in the above study there was uncertainty about the survival of some rats after 7 days, another study was performed in which the rats were observed for 14 days. An aqueous solution of thimerosal, 1%, was given in a range of doses from 62 to 125 mg/kg. The signs of toxicity were the same as described above, and only at the 125 mg/kg dose levels were any deaths recorded before the third day post-treatment.

6

After 7 days the LD_{50} was calculated to be 88.8 ± 5.7 mg/kg, but additional deaths that occurred during the second week resulted in a 14-day LD_{50} of 72.7 ± 5.4 mg/kg.

6

IRRITATION STUDIES

Intraperitoneal

Guinea Pigs: Intraperitoneal injections of 5 ml quantities of thimerosal solutions (0.0125% to 0.1%) were given to guinea pigs.[2] Those receiving the dilute solutions (0.0125% or 0.025%) showed no abnormal response; whereas, those treated with the more concentrated solutions (0.05% or 0.1%) evidenced irritation and pain, and gross autopsy revealed congestion and hemorrhage in the peritoneum.

Intracutaneous

Rabbits: To evaluate the intracutaneous irritancy potential of thimerosal, solutions of 12 different lots of the compound were prepared in 0.01% concentration in physiological saline solution.[3] Each of these solutions was injected intracutaneousl in 0.2 ml volumes into the shaved dorsal skin of 3 New Zealand albino rabbits. Prior to injection the skin was marked into a grid and a random order of injection was made to minimize bias related to location of injection. An evaluation of response was made at 4, 24, 48, and 72 hours post-treatment.

The responses recorded were variable, ranging from no irritation to distinct wheals. Where irritation was noted, it tended to lessen with time so that by 72 hours the margins of the wheals became less distinct. There were no apparent differences between lots.

Guinea Pigs: Using 6 albino femalesthe above experiment was repeated.[3] The test conditions were those described for rabbits except that each guinea pig received only 6 intracutaneous injections, and the volume injected was only 0.1 ml of physiological saline solution containing thimerosal,0.01%. A second experiment was then performed using physiological saline solutions of thimerosal,0.1%.

The response of the guinea pigs to injections of thimerosal, 0.01%, was identified as slight to moderate erythematous wheals. In contrast, the more concentrated solution (0.1%) caused small areas (*ca* 10 mm) of necrosis surrounded by a distinct erythematous wheal.

Although these experiments indicated that the concentrations of thimerosal used were irritating, responses were dose related, and there was no evidence of differences between the 12 lots tested.

9

Subcutaneous

Rabbits: As an extension of the intracutaneous irritation study in rabbits described above, another 3 New Zealand albino rabbits were used to examine the subcutaneous irritancy of 12 lots of thimerosal. Each lot was prepared in 0.01% concentration using physiological saline solution as vehicle. Subcutaneous doses of 0.2 ml were injected into the shaved backs of the animals, using a random injection procedure. After 24 hours there was no evidence of irritation and all three rabbits were killed for evaluation of irritation to subcutaneous tissues. Although most injection sites were free of evidence of subcutaneous injury a few injections had caused small sites of hyperemia. The significance of these few scattered findings was not clear since trauma from needle puncture of small vessels might be the cause of the hyperemia.

Dermal

Rabbits: In studies of dermal irritancy,[3] different lots of thimerosal as Tincture Merthiolate*, containing thimerosal, 0.1%, were applied to the shaved backs of New Zealand albino rabbits. The usual topical application was 0.5 ml and subsequent evaluations of dermal response were made by the method of Draize.

In none of these trials was Tincture Merthiolate shown to be a dermal irritant.

Another study of dermal irritation was performed with an experimental formulation designated Mer-Film. This was an instant dressing containing:

Gantrez AN3152, 33%
Triisopropanolamine, 0.5%
D & C Yellow #7, 0.02%
D & C Red #22, 0.15%
Dimethylphthalate, 1.0%
Silicone Oil DC555, 0.33%
Thimerosal, 0.1%
q.s. Alcohol SP40 to 100%

The samples were applied in 0.5 ml quantities to the shaved backs of New Zealand albino rabbits; 3 rabbits had abraded skin, and 3 were non-abraded. Skin response during the subsequent 72 hours was evaluated by the Draize scoring method.

In this study there was no evidence of dermal irritation.

Ocular

Rabbits: In a study of the irritancy of thimerosal to the eye, Tincture Merthiolate® (thimerosal, 0.1%, in a vehicle of 50% alcohol, 10% acetone) was employed.[3] A volume of 0.1 ml of the tincture was instilled in the right conjunctival sac of 9 New Zealand albino rabbits. The eyes of 3 rabbits remained unrinsed, while the eyes of 3 rabbits were rinsed with water 2 seconds after instillation; the other 3 were rinsed 4 seconds after instillation. Ocular irritation was evaluated 1/2, 1, 2 1/2, 4 1/2, 7, 24, 48, and 72 hours after insult using the scoring method of Draize. In addition, sodium fluorescein was applied at each reading to aid in evaluating corneal injury.

Tincture Merthiolate® in these trials was shown to be a positive eye irritant, damaging both the iris and conjunctiva. Rinse of the eye reduced severity and persistence of irritation. The damage encountered in this study was attributed primarily to the solvent system and is consistent with our experience with eye exposure to alcohol.

Ancill, *et al.*, in studies of mercurialentis used thimerosal in 0.167% and 0.5% concentrations, applying to the right eyes of rats and guinea pigs for one month or longer. Although no corneal toxicity was noted and at no time was mercurialentis observed, these investigators reported measurable levels of mercury in both right and left eyes and in peripheral blood of rats. The values, reported as micrograms mercury/100 mg dry tissue weight are as follows:

	Right Eye (Treated)	Left Eye (Untreated)	Peripheral Blood
Control Rat Cornea	0.111 ± 0.52		0.13
Treated Rat Cornea (0.5% thimerosal)	1.19 ± 0.89	0.16 ± 0.05	1.34

The authors report that the total thimerosal exposure during the period of treatment was 2.65 mg. It should also be noted that the concentration employed in this study (0.5%) was 25 times greater than the concentrations employed in ophthalmic ointment thimerosal, 0.02%. It is also noteworthy that levels of mercury following exposure to the 0.167% thimerosal preparation were unreported. Whether this represents failure to analyze is unknown.

Nakano[6] studied the effects of thimerosal, 0.001%, an effective preservative concentration, on the conjunctiva and cornea of rabbits. No irritation was reported.

SUBACUTE TOXICITY

Intravenous Administration

Dogs: Powell and Jamieson[2] reported that 2 mg/kg of thimerosal was given intravenously every third day to 4 dogs until 12 doses were administered. Necropsy of the dogs 7 days after the last dose revealed no lesions that were not also found in normal dogs.

In another study in dogs, Kinsella and Muether[7] administered thimerosal, 1%, in buffered salt solution to 14 dogs with clinically confirmed experimentally induced bacterial endocarditis. Doses of 1 ml/kg (ca 10 mg thimerosal/kg) were given 6 to 15 days apart for 2 to 5 treatments.

There was no evidence of deaths attributable to thimerosal, and approximately one-half of the animals were cured of the bacterial endocarditis.

Subcutaneous

Rats: Mason and Cate[8] reported giving thimerosal subcutaneously twice weekly to Fisher rats for 18 months. Doses employed were unreported but were based on a single dose LD_{50} and 30 daily doses to permit estimation of the maximally tolerated dose for twice weekly administration for one year.

These investigators reported that after 18 months thimerosal at the highest dose caused a 22% decrease in weight gain, but that lower dose animals were indistinguishable from controls in this regard.

A low incidence of injection site tumors (4%) was correlated with a high incidence of injection site induration and granulomas caused presumably by the local irritation of the compound. The tumors were fibrosarcomas of which none metastasized. Testicular intersitial cell tumors were found in most males that lived to 18 months; a peculiarity of the Fisher rat. Thimerosal caused a dose-related inhibition of these tumors.

SUMMARY

Although toxicity studies of thimerosal in animals are sparse, they tend to confirm the clinical safety record of this compound when used as a topical antiseptic or as a preservative. The most relevant information may be summarized as follows:

1) Given acutely, thimerosal has been shown to have:
   a) Intravenous LD_{50}'s in mice, rats, and rabbits of approximately 25 to 45 mg/kg.
   b) An oral LD_{50} in rats of 72 mg/kg.
   c) The available histopathology of animals that failed to survive thimerosal administration indicated that death resulted (usually within 3-9 days post-treatment) from kidney and gastrointestinal lesions consistent with mercury poisoning.
2) In irritation studies conducted by a variety of routes (intraperitoneal, intracutaneous, subcutaneous, dermal, and ocular) in several animal species thimerosal has been shown to be an irritant when concentrations are sufficiently high. It is noteworthy that dermal irritation is not detected at a concentration of 0.1%, the usual antiseptic concentration.

3) In a study of mercury absorption from the eyes of rats treated for 30 days with a preparation containing thimerosal, 0.5%, a significant absorption of mercury was noted. This level of exposure was, however, 25 times greater than that present in the usual ophthalmic preparation of thimerosal. It should also be mentioned that even at this abusive level corneal damage and mercurialentis could not be shown.

4) In subacute toxicity trials in rats (18 months given subcutaneously twice weekly) and in dogs (2-5 intravenous doses of 10 mg/kg spaced 6 to 15 days apart or 12 doses of 2 mg/kg spaced 3 days apart) thimerosal was well tolerated.

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19